MEDICAL EMBRYOLOGY

INTRODUCTION

Human Embryology is the study of developmental anatomy from a single cell to a baby in 9 months. Medical embryology includes clinical aspects that interfere with normal embryology

Age of Fetus

A "full-term" human pregnancy ranges from 216 to 306 days with a modal length of **266** days. **Fertilization age** of the fetus uses the event of fertilization as time zero. **Menstrual age** uses the start of the mother's last normal menstrual period (LNMP) as time zero, meaning that **menstrual age is approximately two weeks older than fertilization age**.

PRE-FERTILIZATION EVENTS

Gametogenesis

Gametes

Normal **somatic** human cells are **diploid** possessing a **2N** amount of DNA in the form of 46 chromosomes arranged in **23 homologous pairs**. One chromosome in each homologous pair comes from each parent. Of these chromosomes **44** are **autosomal** and 2 are sex chromosomes. Somatic cells reproduce by normal cell division known as **mitosis,** which yields daughter cells also with a 2N amount of DNA. The daughter cells produced by mitosis are genetically identical.

Gametes (**oocytes** and **spermatozoa**) are the descendants of **primordial germ cells** that originate in the **wall of the yolk sac** in the embryo and migrate to the gonadal region. Gametes are specialized **haploid** reproductive cells possessing **1N** amount of DNA in the form of 22 autosomal chromosomes and one sex chromosome for a total of 23 chromosomes.

Mitosis and Meiosis

Primordial germ cells differentiate into gametes by a specialized two-phase cell division process known as **meiosis**, which produces four haploid (1N) cells from one diploid (2N) germ cell. **Replication of DNA** and **crossover** occur during **meiosis I**. **Centromeric division** (and reduction of chromosome number) occurs during **meiosis II**. The random distribution of chromosomes between the resulting daughter cells in this process results in the**independent assortment of chromosomes**, and together with **crossover** are mechanisms for ensuring genetic variability among offspring.

Female Gametogenesis (Oogenesis)

In females, most of gametogenesis occurs during embryonic development. Primordial germ cells migrate into the ovaries at week 4 of development and differentiate into **oogonia** (46,2N). Oogonia enter **meiosis I** and undergo DNA replication to form **primary oocytes** (2N,4C). **All primary oocytes are formed by the fifth month of fetal life and remain dormant in prophase of meiosis I until puberty**.

During a woman's ovarian cycle one oocyte is selected to complete meiosis I to form a **secondary oocyte** (1N,2C) and a **first polar body**. After **ovulation** the oocyte is arrested in **metaphase of meiosis II** until fertilization. At **fertilization**, the secondary oocyte completes meiosis II to form a **mature oocyte** (23,1N) and a **second polar body**.

Male Gametogenesis (Spermatogenesis)

In males, gametogenesis begins at puberty and continues into advanced age. Primordial germ cells (46,2N) migrate into the testes at week 4 of development and remain dormant. At puberty, primordial germ

cells differentiate into **type A spermatogonia** (46,2N). Type A spermatogonia divide by **mitosis** to form either more type A spermatogonia (to maintain the supply) or **type B spermatogonia**.

Gamete Transport

Ovulation

Under the influence of **estrogen released during the first half of the menstrual cycle**, three changes take place in the uterine tubes to facilitate its capture of the egg:

1. The uterine tubes move closer to the ovaries (**physical approximation**)
2. The fimbriae on the ends of the tubes beat more rapidly (**increased fluid current**)
3. The number of ciliated cells in the epithelium of the fimbriae increase (**increase in ciliation**)

Transport of Sperm in Female

Sperm are deposited in the upper vagina and must overcome several obstacles to reach an egg in the ampulla of one of the uterine tubes.

Sperm lose their ability to fertilize an egg after **3 - 3½ days**. The egg itself is viable for only about **24 hours**.

Table 1 - Obstacles to Sperm Transport

Obstacle	**Adaptation**
Low pH of upper vagina	The **alkaline seminal fluid** temporarily neutralizes the normal acidity (pH 4.3 □ pH 7 – 7.2) to allow the sperm to survive in the upper vagina.
Cervical mucus	The composition of **cervical mucus changes**during menstrual cycle. Sperm can most easily penetrate the thinner **E-mucus** that predominates during the last few days before ovulation, as opposed to the thicker **G-mucus**.
Cervical canal, uterus	Two modes of transport: **Rapid** – some sperm travel from the vagina to the upper 1/3 of the uterine tube in as little as 30 minutes. Since sperm normally swim only 2-3 mm/hr, it is thought that they are actively transported by smooth muscle contractions of the female or some other mechanism. **Slow** – the rest of the sperm swim their way up the last part of the cervical tube, are stored in cervical crypts (folds of the cervix), and are slowly released into the uterus over 2-3 days.

Table 2 - Karyotypes of Germ Cells and Gametes

Cell	**Karyotype**
Primordial germ cell	46,2N
Female	
Oogonium	46,2N
Primary oocyte	46,4N
Secondary oocyte	23,2N
Mature oocyte	23,1N
Male	
Type A spermatogonium	46,2N
Type B spermatogonium	46,2N
Primary spermatocyte	23,2N
Secondary spermatocyte	23,1N
Spermatid	23,1N

Clinical Correlations

Aneuploidy

Aneuploidy is an abnormal number of chromosomes that can result from either **unbalanced chromosomal translocations** or **nondisjunction during meiosis II**. Most chromosomal abnormalities are incompatible with life, however, some combinations do result in live offspring, and trisomies involving chromosomes 13, 14, 15, 21 and 22 (groups D and G chromosomes) are relatively common birth defects. **Down syndrome** results from **trisomy 21** that occurs in approximately **1/500** live births, and is characterized by growth retardation, mental retardation, and specific somatic abnormalities. **Aneuploidy of the sex chromosomes** can also occur, and certain karyotypes are associated with characteristic syndromes.

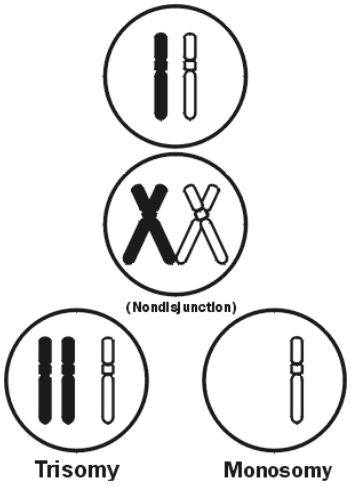


Table 3 - Syndromes Associated with Aneuploidy of the Sex Chromosomes

Karyotype	Syndrome	Frequency	Description
45,X (XO)	Turner syndrome	1/5000 female live births	Phenotypic female, gonadal dysgenesis and sexual immaturity after puberty, infertility
XXY	Klinefelter's syndrome	1/1000 male live births	Phenotypic male, gonadal dysgenesis and sexual immaturity after puberty, infertility
XYY (XXYY)	XYY syndrome	1/1000 male live births	Phenotypic male, behavioral abnormalities

FIRST WEEK (DAY 1-7)

Fertilization

After ovulation, the unfertilized egg is arrested in **prophase of meiosis II** and contains **one polar body** left over from meiosis I. Fertilization is a process of several events and typically takes place in the **ampullated portion of the uterine tube**:

Capacitation

Changes take place in the glycoprotein coat of sperm as they travel up the female reproductive tract. These changes are absolutely essential for fertilization. Thus, to perform successful *in vitro* fertilization you must add some tissue extracted from the female reproductive tract in addition to the sperm and egg extracted from the parents.

Approximation

Only a tiny fraction of sperm actually reaches the ampulla of the uterine tube to be near the egg.

Penetration of Corona Radiata

The sperm uses both chemical and physical means to penetrate the egg's corona radiata:

- The action of membrane-bound enzyme hyaluronidase on its coat, and
- Swimming motion of its flagellum.

Penetration of Zona Pellucida

Once inside the corona radiata, the sperm binds to the species-specific ZP3 receptor on the egg's glycoprotein coat. This triggers the **acrosomal reaction**, or the release of enzymes stored in the sperm's acrosome (e.g. acrosin). These enzymes help the sperm "drill through" the zona pellucida.

Once the sperm has penetrated the outer layers it fuses with the plasma membrane of the egg and releases its contents inside. The head and the tail of the sperm degrade, so that **all mitochondria in the embryo (and all mitochondrial DNA) come from the mother**.

Cortical Reaction

Entry of a sperm into the egg triggers changes that prevent polyspermy (fertilization of an egg by more than one sperm). These changes are known as the **cortical reaction**.

Table 4 - Cortical Reaction

Phase	Description
Fast block	**Electrical depolarization of the egg's surface** (–70Mv +10Mv) works for a short time to repel other sperm electrostatically.
Slow block	A wave of Ca^{++} ions released from the point of sperm entry spreads through the egg. This causes **cortical granules in the egg to release their contents**. Polysaccharides in the cortical granules reach the outside of the egg and form a physical barrier to sperm penetration. Enzymes in the granules break down the ZP3 receptors in the zona pellucida and also further harden the coat.

Fusion of Pronuclei

DNA in the male pronucleus is packed very tightly with protamines to make it compact enough to fit inside a sperm. These protamines are replaced by histones inside the egg, unpacking the DNA. Afterwards the male and female pronuclei fuse and the egg completes its second meiotic division, resulting in a second **polar body**. The fertilized egg is now known as the **zygote** ("together").

Cleavage

The zygote undergoes a number of **ordinary mitotic divisions** that increase the number of cells in the zygote but not its overall size. Each cycle of division takes about 24 hours. The individual cells are known as **blastomeres**. At the 32-cell stage the embryo is known as a **morula** (L. "mulberry"), a solid ball consisting of an **inner cell mass** and an **outer cell mass**. The **inner cell mass** will eventually become the **embryo and fetus**, while the **outer cell mass** will eventually become part of the **placenta**.

Blastocyst Formation

Compaction

The **cells on the outside of the morula form tight intercellular junctions** and express ion channels to create an impermeable barrier.

Cavitation

A fluid-filled cavity forms inside the morula. This cavity is known as the **blastocyst cavity** or **blastocoele**, and the morula is now called a **blastula** or **blastocyst**. The inner cell mass is now known as the **embryoblast** and the outer cell mass becomes the **trophoblast**.

Implantation

Hatching

The blastula sheds its zona pellucida. This is required for implantation to occur. One function of the zona pellucida is to prevent premature implantation.

Attachment and Invasion

The embryo attaches to and invades into the maternal endometrium. The trophoblast differentiates into the **cytotrophoblast** and the **syncytiotrophoblast**. The **embryo typically implants in the posterior superior wall of the uterus**. The response of the maternal endrometrial cells to the invading embryo is called the **decidual reaction**.

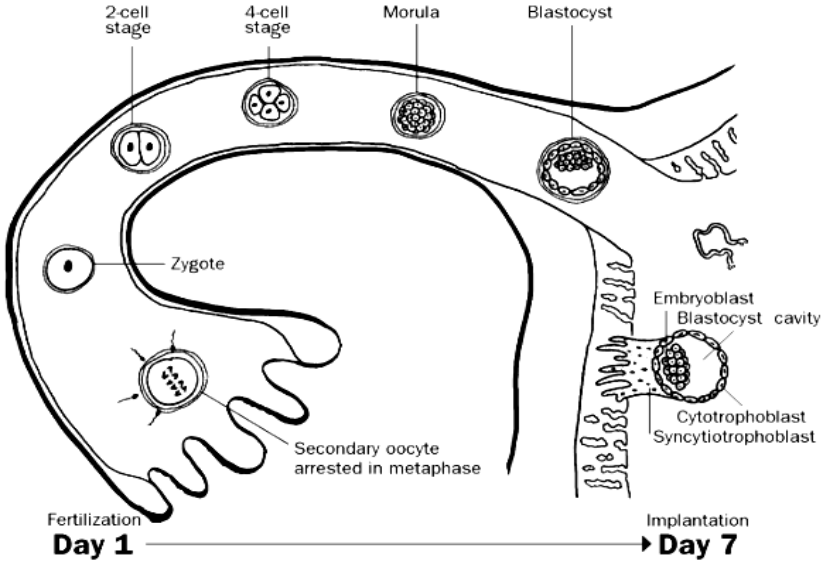


Figure 1 - Summary of the first week of development

Clinical Correlations

Ectopic pregnancy

The bastocyst implants in a location other than the uterus. This can present as an acute surgical emergency for the mother after the fetus begins to outgrow its confines:

Table 5 - Common Sites of Ectopic Pregnancy

Site of implantation	Likely reason
Upper and middle part of the uterine tube	Embryo probably lost its zona pellucida prematurely. Most common ectopic location.
Ovary	The egg was never released from the ovary.
Abdominal cavity	Probably caused by defect in egg capture process. Rarely, an asymptomatic ectopic fetus can die and calcify to become a **lithopedeon** (“stone baby”).

Placenta Previa

The embryo implants in the **lower part of the uterus towards the cervix**. This makes it easy for the placenta to tear, and the mother can die from hemorrhage, or the placenta may grow to obstruct the cervical canal. This is diagnosed with ultrasound, and the baby is delivered via Cesarean section.

SECOND WEEK (DAY 8-14)

Trophoblast

As the blastocyst embeds itself in the endrometrium it differentiates into two layers: the **cytotrophoblast** (inner) and **syncytiotrophoblast** (outer). The syncytiotrophoblast invades into the maternal endrometrium, and in this sense it is more invasive than any tumor tissue. As it comes into contact with blood vessels it creates **lacunae**, or spaces which fill with maternal blood. These lacunae fuse to form **lacunar networks**. The maternal blood that flows in and out of these networks exchanges nutrients and waste products with the fetus, forming the basis of a **primitive uteroplacental circulation**.

Syncytiotrophoblast

The syncytiotrophoblast is **acellular** and does not expand mitotically. The syncytiotrophoblast produces **human chorionic gonadotrophin** (hCG), a glycoprotein hormone that stimulates the production of **progesterone** by the **corpus luteum**.

Cytotrophoblast

The **cytotrophoblast** is cellular and expands mitotically into the syncytiotrophoblast to form **primary chorionic villi**. Cells from these villi can be removed for early genetic testing at some risk to the fetus (**chorionic villus sampling**).

Embryoblast

After implantation, the **inner cell mass** subdivides into a bilaminar disc consisting of the **hypoblast** and **epiblast**.

Hypoblast

Hypoblast cells migrate along the inner surface of the cytotrophoblast and will form the **primary yolk sac**. The primary yolk sac becomes reduced in size and is known as the **secondary yolk sac**. In humans the yolk sac **contains no yolk** but is important for the transfer of nutrients between the fetus and mother.

Epiblast

Epiblast cells cavitate to form the **amnion**, an extra-embryonic epithelial membrane covering the embryo and amniotic cavity. Cells from the epiblast will also eventually form the **body** of the embryo.

Extra-embryonic mesoderm

Extra-embryonic mesoderm cells migrate between the cytotrophoblast and yolk sac and amnion. **Extraembryonic somatic mesoderm** lines the cytotrophoblast and covers the amnion is. Extraembryonic somatic mesoderm also forms the **connecting stalk** that is the primordium of the **umbilical cord**. **Extraembryonic visceral mesoderm** covers the yolk sac.
At the end of the second week it is possible to distinguish the dorsal (amniotic cavity) from the ventral (yolk sac) side of the embryo.

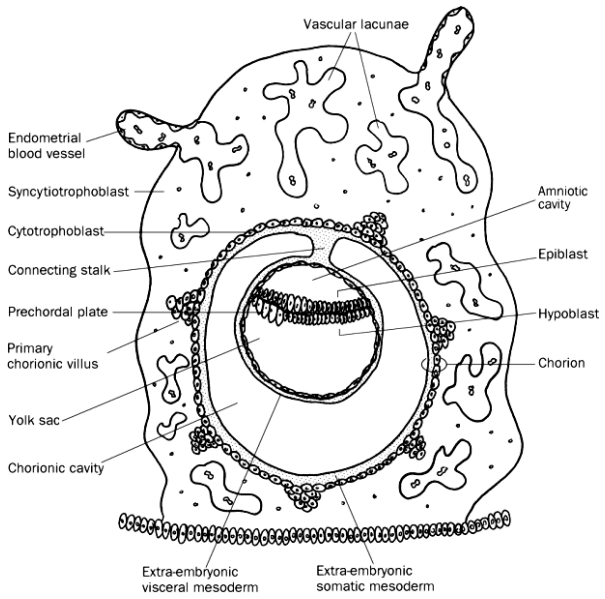


Figure 2 - Day 14 blastocyst showing structure of the placenta

Clinical Correlations

Early pregnancy testing

hCG produced by the syncytiotrophoblast can be detected in maternal blood or urine as early as **day 10** of pregnancy and is the basis for pregnancy tests.

Hydatidiform mole

A blighted blastocyst leads to death of the embryo, which is followed by hyperplastic proliferation of the trophoblast within the uterine wall.

Choriocarcinoma

A malignant tumor arising from trophoblastic cells that may occur following a normal pregnancy, abortion, or a hydatidiform mole.

EMBRYONIC PERIOD (WEEK 3-8)

Gastrulation

Gastrulation is the conversion of the epiblast from a bilaminar disc into a **trilaminar embryonic disc** consisting of **ectoderm**, **mesoderm**, and**endoderm**. Gastrulation begins with the formation of the **primitive streak**.

Primitive Streak

The **primitive streak** is a **linear band of thickened epiblast** that first appears at the **caudal** end of the embryo and **grows cranially**. At the cranial end its cells proliferate to form the **primitive knot** (**primitive node)**. With the appearance of the primitive streak it is possible to distinguish cranial (primitive knot) and caudal (primitive streak) ends of the embryo.

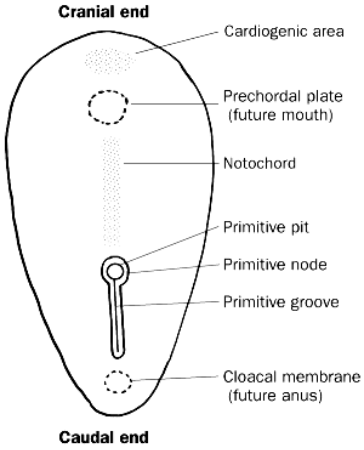


Figure 3 - Primitive streak and notochord

Notochordal Process

Mesenchymal cells migrate from the primitive knot to form a midline cellular cord known as the **notochordal process**. The notochordal process grows cranially until it reaches the prechordal plate, the future site of the **mouth**. In this area the ectoderm is attached directly to the endoderm without intervening mesoderm. This area is known as the **oropharyngeal membrane**, and it will break down to become the **mouth**. At the other end of the primitive streak the ectoderm is also fused directly to the endoderm; this is known as the **cloacal membrane** (**proctodeum)**, or primordial **anus**.

Notochord

The notochord is a cellular chord that develops by transformation of the notochordal process. The notochord will eventually become the *nucleus pulposis* of each intervertebral disk.

Germ layers

The embryonic three germ layers give rise to the many tissues and organs of the embryo:

Table 6 - Embryonic Germ Layers and Their Adult Derivatives

Germ Layer		**Adult Derivatives**
Ectoderm	Surface ectoderm	Lens of eye Adenohypophysis (anterior pituitary gland) Utricle, semicircular ducts, and vestibular ganglion of CN VIII Epithelial lining of external auditory meatus Olfactory placode, including CN I Epithelial lining of: anterior two thirds of tongue, the hard palate, sides of the mouth, ameloblasts, and parotid glands and ducts Mammary glands Epithelial lining of lower anal canal Epithelial lining of distal penile urethra Epidermis, hair, nails, sweat and cutaneous sebaceous glands
	Neuroectoderm	All neurons within the CNS All glial (supporting) cells within the CNS Retina Pineal gland Neurohypophysis (posterior pituitary gland)
	Neural crest	Postganglionic sympathetic neurons within the sympathetic chain ganglia

		and prevertebral ganglia Postganglionic parasympathetic neurons within the ciliary, pterygopalatine, submandibular, otic, enteric ganglia, and ganglia of the abdominal and pelvic cavities Sensory neurons within the dorsal root ganglia, Schwann cells Pia mater and arachnoid membrane Chromaffin cells of the adrenal medulla Melanocytes Bony structures of the face and neck: Maxilla, zygomatic bone, palatine bone, vomer, mandible, hard palate, incus, malleus, stapes, sphenomandibular ligament, styloid process, stylohyoid ligament, hyoid bone, frontal bone, parietal bond, sphenoid bone, and ethmoid bone Odontoblasts Aorticopulmonary septum Parafollicular cells of thyroid Dilator and sphincter pupillae muscles Ciliary muscle Carotid body
Mesoderm	Paraxial mesoderm	Skeletal muscles of trunk Skeletal muscles of limbs Skeletal muscles of head and neck Extraocular muscles Intrinsic muscles of tongue Vertebrae and ribs Cranial bone Dermis Dura mater
	Intermediate mesoderm	Kidneys Testes and ovaries Genital ducts and accessory sex glands
	Lateral mesoderm	Sternum, clavicle, scapula, pelvis, and bones of the limbs Serous membranes of body cavities Lamina propria, muscularis mucosae, submucosa, muscularis externae, and adventitia of the gastrointestinal tract Blood cells, microglia, Kupffer cells Cardiovascular system Lymphatic system Spleen Suprarenal cortex Laryngeal cartilages
Endoderm		Epithelial lining of the auditory tube and middle ear cavity Epithelial lining of the posterior third of the tongue, floor of the mouth, palatoglossal and palatopharyngeal folds, soft palate, crypts of the palatine tonsil, and sublingual and submandibular glands and ducts Principal and oxyphil cells of the parathyroid glands Epithelial reticular cells and thymic corpuscles

		Thyroid follicular cells Epithelial lining and glands of the trachea, bronchi, and lungs Epithelial lining of the gastrointestinal tract Hepatocytes and epithelial lining of the biliary tree Acinar cells, islet cells, and the epithelial lining of the pancreatic ducts Epithelial lining of the urinary bladder Epithelial lining of the vagina Epithelial lining of the female urethra and most of the male urethra

Development of Somites

As the notochord and neural tube form, the mesoderm alongside them forms longitudinal columns called **paraxial mesoderm**. These columns divide into paired cubical bodies called **somites**. The somites develop in pairs; the first pair develops near the cranial end of the notochord around the end of the third week. Additional pairs of somites develop in a caudal direction from days 20 to 30 (**period of somite development**) and the number of somites is sometimes used as a criterion for determining an embryo's age. The somites give rise to most of the axial skeleton (vertebral column, ribs, sternum, and skull base) and associated musculature, as well as to the adjacent dermis.

PLACENTA AND EXTRAEMBRYONIC MEMBRANES

Placenta

The placenta is a fetomaternal organ. The fetal portion of the placenta is known as the **villous chorion**. The maternal portion is known as the **decidua basalis**. The two portions are held together by **anchoring villi** that are anchored to the decidua basalis by the cytotrophoblastic shell.

Decidua

The endometrium (lining of the uterus) of the mother is known as the **decidua** ("cast off"), consisting of three regions named by location.

Table 7 - Regions of the Decidua

Region	Description
Decidua basalis	Region between the blastocyst and the myometrium
Decidua capsularis	Endometrium that covers the implanted blastocyst
Decidua parietalis	All the remaining endometrium

As the embryo enlarges, the decidua capsularis becomes stretched and smooth. Eventually the decidua capsularis merges with the decidua parietalis, obliterating the uterine cavity.

Placental Membrane

Function

The **placental membrane** separates maternal blood from fetal blood. The fetal part of the placenta is known as the **chorion**. The maternal component of the placenta is known as the **decidua basalis**.

- **Oxygen and nutrients** in the maternal blood in the intervillous spaces diffuse through the walls of the villi and enter the fetal capillaries.

- **Carbon dioxide and waste products** diffuse from blood in the fetal capillaries through the walls of the villi to the maternal blood in the intervillous spaces.

The Placenta

Although the placental membrane is often referred to as the **placental barrier**, many substances, both helpful and harmful, can cross it to affect the developing embryo.

Structure

- **Primary chorionic villi are solid** outgrowths of cytotrophoblast that protrude into the syncytiotrophoblast.
- **Secondary chorionic villi have a core of loose connective tissue**, which grows into the primary villi about the third week of development.
- **Tertiary chorionic villi contain embryonic blood vessels** that develop from mesenchymal cells in the loose connective tissue core. These blood vessels connect up with vessels that develop in the chorion and connecting stalk and begin to circulate embryonic blood about the **third week** of development.

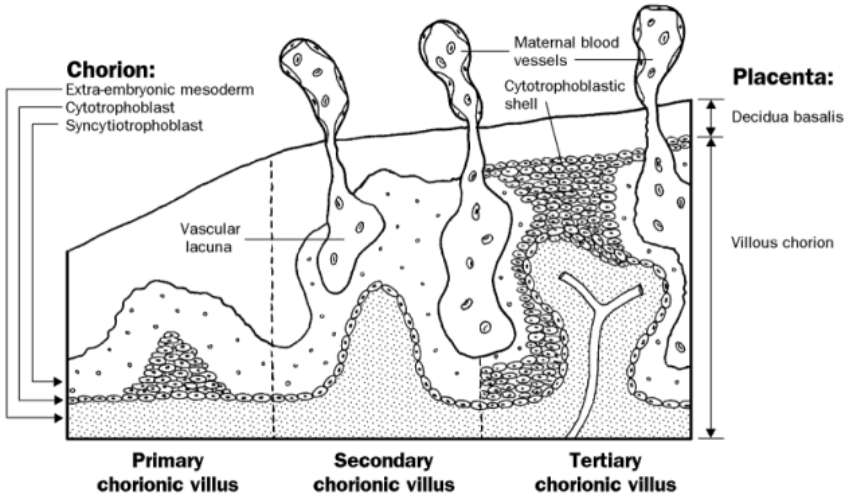


Figure 4 - Structure of placenta and chorionic villi

Table 8 - Substances that Cross the Placental Membrane

Substances	Examples
Beneficial	
Gases	Oxygen, carbon dioxide
Nutrients	Glucose, amino acids, free fatty acids, vitamins
Metabolites	Carbon dioxide, urea, uric acid, bilirubin, creatine, creatinine
Electrolytes	Na^+, K^+, Cl^-, Ca^{2+}, PO_4^{2-}
Erythrocytes	Fetal and maternal both (a few)
Maternal serum proteins	Serum albumin, some protein hormones (thyroxin, insulin)
Steroid hormones	Cortisol, estrogen (unconjugated only)
Immunoglobins	IgG (confers fetal passive immunity)
Harmful	
Poisonous gases	Carbon monoxide

Infectious agents	Viruses (HIV, cytomegalovirus, rubella, Coxsackie, variola, varicella, measles, poliomyelitis), bacteria (tuberculosis, *Treponema*), and protozoa (*Toxoplasma*)
Drugs	Cocaine, alcohol, caffeine, nicotine, warfarin, trimethadione, phenytoin, tetracycline, cancer chemotherapeutic agents, anesthetics, sedatives, analgesics
Immunoglobins	Anti-Rh antibodies

Amniotic Fluid

Amniotic fluid has three main functions: it protects the fetus physically, it provides room for fetal movements, and helps to regulate fetal body temperature. Amniotic fluid is produced by **dialysis of maternal and fetal blood** through blood vessels in the placenta. Later, production of **fetal urine** contributes to the volume of amniotic fluid and **fetal swallowing** reduces it. The water content of amniotic fluid turns over every three hours.

Umbilical Cord

The umbilical cord is a composite structure formed by contributions from:

- Fetal connecting (body) stalk
- Yolk sac
- Amnion

The umbilical cord contains the **right** and **left umbilical arteries**, the **left umbilical vein**, and mucous connective tissue. Presence of only one umbilical artery may suggest the presence of cardiovascular anomalies.

Fetal Circulation

Fetal circulation involves three circulatory shunts: the **ductus venosus**, which allows blood from the placenta to **bypass the liver**, and the **ductus arteriosus** and **foramen ovale**, which together allow blood to **bypass the developing lungs**. Refer to the section on changes at birth for more information on the fates of these structures.

Clinical Correlations

Multiple Pregnancy

Dizygotic twins are derived from two zygotes that were fertilized independently (i.e., two oocytes and two spermatozoa). Consequently, they are associated with two amnions, two chorions, and two placentas, which may (65%) or may not (35%) be fused. Dizygotic twins are only as closely genetically related as any two siblings.

Monozygotic twins (30%) are derived from one zygote that splits into two parts. This type of twins commonly has two amnions, one chorion, and one placenta. If the embryo splits early in the second week after the amniotic cavity has formed, the twins will have one amnion, one chorion, and one placenta. Monozygotic twins are genetically identical, but may have physical differences due to differing developmental environments (e.g., unequal division of placental circulation).

Placenta Previa

The fetus implants in such a way that the placenta or fetal blood vessels grow to block the internal os of the uterus. See **implantation**.

Erythroblastosis Fetalis

Some erythrocytes produced in the fetus routinely escape into the mother's systemic circulation. When fetal erythrocytes are Rh-positive but the mother is Rh-negative, the mother's body can form antibodies to

the Rh antigen, which cross the placental barrier and destroy the fetus. The immunological memory of the mother's immune system means this problem is much greater with second and subsequent pregnancies.

Oligohydramnios

Deficiency of amniotic fluid (less than 400 ml in late pregnancy). It can result from **renal agenesis** because the fetus is unable to contribute urine to the amniotic fluid volume.

SYSTEMIC EMBRYOLOGY

Muskuloskeletal Development

Towards the end of the fourth week the limbs begin to develop from **limb buds** made up of mesenchyme (**somatic mesoderm**) covered with **surface ectoderm**. The **apical ectodermal ridge** at the tip of each limb bud induces the mesenchyme beneath it to elongate. At the end of each limb the hand or foot first develops as a single flat outgrowth, then programmed death of selective cells (apoptosis) causes it to divide into distinct digits.

Movement of Limbs

Initially the limbs develop high on the trunk where they are supplied by the ventral rami of adjacent spinal nerves. Spinal roots **C5 – T1** supply the upper limb bud and **L2 – S3** supply the lower limb bud. During weeks six through eight the limbs descend to their adult height taking their nerve supply with them. To attain adult anatomical position, the upper and lower limbs rotate in opposite directions and to different degrees, with the result that the adult elbow points posteriorly and the adult knee points anteriorly.

Skeletal Elements

Cartilaginous bones begin to develop from **chondrification centers** early in the fifth week. Ossification of the long bones (**osteogenesis**) begins from **primary ossification centers**, which appear in the middle of the long bones in the seventh week. Ossification of the carpal (wrist) bones does not begin until approximately the first year after birth. The skeletal muscle of the limbs is derived from myotomal cells that migrate into the limbs, followed by the branches of their associated spinal nerves.

Clinical Correlations

Limb Malformations

Amelia is complete absence of one or more limbs. **Phocomelia** is a defect wherein the upper portion of a limb is absent or poorly developed, so that the hand or foot attaches directly to the body by a short, flipperlike stump. These defects are often due to a failure of inductive signaling factors, and may inherit in a Mendelian fashion.

Malformations of Hands and Feet

Syndactyly is congenital anomaly characterized by two or more fused fingers or toes. **Macrodactyly** (**megadactyly**) is enlargement of one or more digits. **Polydactyly** is a condition wherein there are extra digits, whereas in **ectrodactyly** there are fewer than normal.

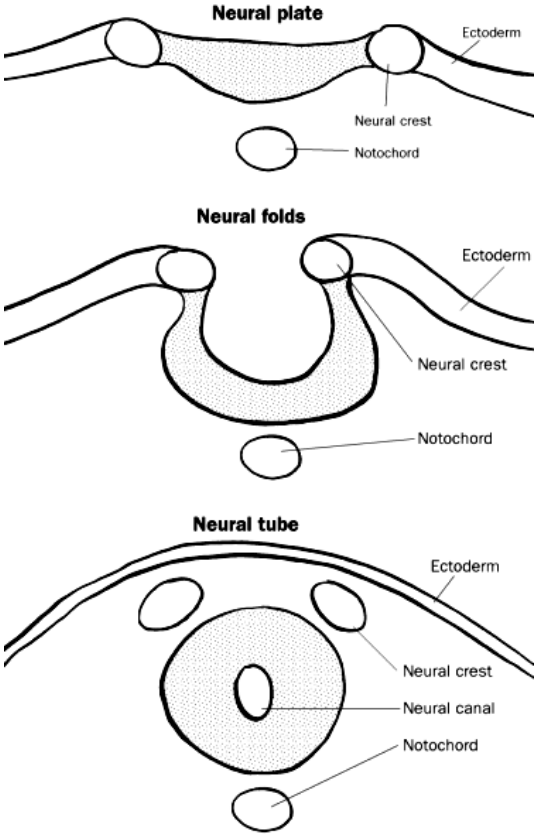
Clubfoot (talipes equinovarus)

Clubfoot is a common foot malformation (1/5,000 infants) characterized by **abnormal positions of the foot** (e.g., inverted). Some cases result from compression of the infant in the uterus (e.g., with **oligohydramnios**)

Achondroplasia

One form of **congenital dwarfism** resulting from improper development of cartilage at the ends of the long bones.

Neurulation



Neural Tube

The nervous system develops when the **notochord** induces its overlying ectoderm to become **neuroectoderm** and to develop into the **neural plate**. The neural plate folds along its central axis to form a **neural groove** lined on each side by a **neural fold**. The two neural folds fuse together and pinch off to become the **neural tube**. Fusion of the neural folds begins in the middle of the embryo and moves cranially and caudally. The **cranial** open end of the tube is the **anterior (rostral) neuropore**, and the **caudal** open end of the tube is the **posterior (caudal) neuropore**. The anterior neuropore closes on or before **day 26** and the caudal neuropore closes before the **end of the fourth week**.

Neural Crest

Some cells from the **neural folds** give rise to pleuripotent **neural crest** cells that migrate widely in the embryo and give rise to many nervous structures:

- Spinal ganglia (dorsal root ganglia)
- Ganglia of the autonomic nervous system
- Ganglia of some cranial nerves
- Sheaths of peripheral nerves
- Meninges of brain and spinal cord
- Pigment cells
- Suprarenal medulla
- Skeletal and muscular components in the head

Central Nervous System

Development of Brain

The neural tube forms three **primary brain vesicles**. The primary brain vesicles give rise to five **secondary brain vesicles**, which give rise to various adult structures.

Primary vesicles	Secondary vesicles	Adult structures
Forebrain vesicle (**prosencephalon**)	Telencephalon	Cerebral hemispheres, consisting of the cortex and medullary center, basal ganglia, lamina terminalis, hippocampus, the corpus striatum, and the olfactory system
	Diencephalon	Thalamus, epithalamus, hypothalamus, subthalamus, neurohypophysis, pineal gland, retina, optic nerve, mamillary bodies
Midbrain vesicle (**mesencephalon**)	Mesencephalon	Midbrain
Hindbrain vesicle (**rhombencephalon**)	Metencephalon	Pons and cerebellum
	Myelencephalon	Medulla

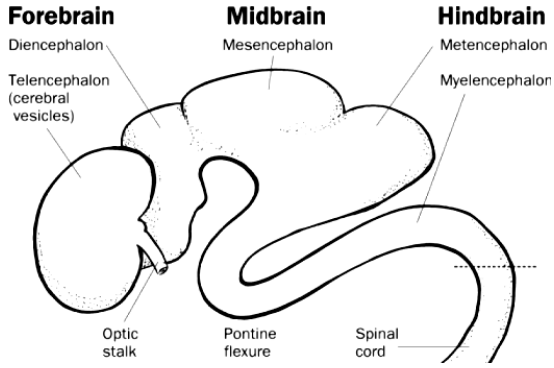


Figure 5 - Structure of embryonic brain

Development of Spinal Cord

The neural tube consists of three cellular layers from inner to outer: the **ventricular zone** (ependymal layer), the **intermediate zone** (mantle layer), and the **marginal zone** (marginal layer). The **ventricular zone** gives rise to **neuroblasts** (future nerve cells) and **glioblasts** (future supporting cells) which **migrate** into the intermediate zone form two collections of cells (the **alar plate** and the **basal plate**) separated by a groove called the **sulcus limitans**. Cells in the **alar plate** become **afferent** (**sensory**) **neurons** and form the **dorsal (posterior) horn** of the spinal cord. Cells in the **basal plate** become **efferent** (**motor**) **neurons** and form the **ventral (anterior) horn** of the spinal cord. The two ventral horns bulge ventrally to create **ventral median fissure**. The dorsal horns merge to create the **dorsal median septum**. The lumen of the neural tube becomes the **central canal** of the spinal cord.

The spinal cord extends the entire length of the vertebral canal at **week 8** of development. At **birth**, the conus medullaris extends to the **L3** vertebra. In the **adult**, the conus medullaris extends to the **L1** vertebra. **Spinal lumbar punctures** must be performed caudally to the conus medullaris to avoid damaging the spinal cord.

Development of Meninges

The **dura mater** arises from **paraxial mesoderm** that surrounds the neural tube. The **pia mater** and **arachnoid mater** arise from **neural crest** cells.

Hypophysis (Pituitary Gland)

The **anterior pituitary gland** (***adenohypophysis***) arises from an evagination of the **oropharyngeal membrane** known as **Rathke's pouch**. The **posterior pituitary gland** (***neurohypophysis***) arises from an evagination of **neuroectoderm** from the **diencephalon**.

Clinical Correlations

Spina Bifida

· **Spina bifida occulta** is a defect of the vertebral column only, and is a common problem affecting as many as 10% of live births.

· **Spina bifida with meningocele** (spina bifida cystica) is a defect of the vertebral column with protrusion of the meninges through the defect.

· **Spina bifida with myelomeningocele** is a defect of the vertebral column protrusion of the meninges and herniation of the spinal cord through the defect.

· **Spina bifida with myeloschisis** results from the failure of the caudal neuropore to close at the end of the fourth week of development. Newborn infants are paralyzed distal to the lesion.

These defects usually occur in the cervical and/or lumbar regions and may cause neurologic deficits in the lower limbs and urinary bladder. Neural tube defects can be detected by the presence of **alpha-fetoprotein** (AFP) in the fetal circulation after the fourth week of development.

Anencephaly

Anencephaly is the failure of the anterior neuropore to close, resulting in a failure of the brain to develop.

Microcephaly

Microcephaly (small head) results from microencephaly (small brain), or the failure of the brain to grow normally. This can be the result of exposure to large doses of radiation up to the sixteenth week of development, or from certain infectious agents (cytomegalovirus, herpes simplex virus, *and toxoplasma gondii*)

Hydrocephalus

Hydrocephalus is an accumulation of CSF in the ventricles of the brain, caused most commonly by stenosis of the cerebral aqueduct. In the absence of surgical treatment in extreme cases the head may swell to three times its normal size.

Arnold-Chiari Malformation

Arnold-Chiari malformation is herniation parts of the cerebellum (medulla oblongata and cerebellar vermis) through the **foramen magnum** of the skull.

Fetal Alcohol Syndrome

Ingestion of alcohol during pregnancy is the most common cause of infant **mental retardation**. It also causes **microcephaly** and **congenital heart disease**.

Branchial Apparatus

The **branchial** (Gk. gill) **apparatus** of a four-week-old embryo consists of the **branchial arches**, **pouches**, **grooves** (clefts), and **membranes**.

Each branchial arch (1, 2, 3, 4 and 6) is composed of **lateral mesoderm** and **neural crest cells** and each is associated with a **cranial nerve** and an **aortic arch**.

Table 9 - Adult Derivatives of Pharyngeal Arches

		Adult Derivatives	
Arch	Nerve	Muscles (Mesoderm)	Skeletal Structures (Neural Crest)
First (mandibular)	Trigeminal (CN V)	Muscles of mastication, mylohyoid muscle tensor veli palitini muscle, tensor tympani muscle, anterior belly of the digastric muscle	Maxilla, zygomatic bone, temporal bone, palatine bone, vomer, mandible, malleus, incus, sphenomandibular ligament
Second (hyoid)	Facial (CN VII)	Muscles of facial expression, stylohyoid muscle, stapedius muscle posterior belly of digastric muscle	Stapes, styloid process, stylohyoid ligament, lesser horn and superior body of the hyoid bone
Third	Glossopharyngeal (CN IX)	Stylopharyngeus muscle	Greater horn and inferior body of the hyoid bone
Fourth	Vagus (CN X) – Superior laryngeal branch	Muscles of soft palate (except tensor veli palatini) and muscles of pharynx (except stylopharyngeus), cricothyroid muscle, cricopharyngeus muscle,	Thyroid cartilage, cricothyroid cartilage, arytenoid cartilage, laryngeal cartilages
Sixth[1]	Vagus (CN X) – Recurrent laryngeal branch	Intrinsic muscles of the larynx (except cricothyroid), upper (skeletal) muscles of esophagus	Laryngeal cartilages

Table 10 - Adult Derivatives of Pharyngeal Pouches

Pouch	**Adult derivatives**
1	Lining of **auditory tube** and **tympanic cavity** (middle ear cavity)
2	Largely obliterated, lining of **intratonsillar cleft** (tonsilar fossa)
3	Inferior parathyroid glands, thymus
4	Superior parathyroid glands, parafollicular cells of thyroid gland

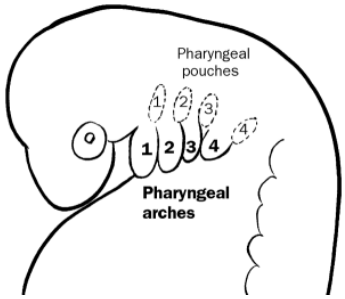


Figure 6 - Pharyngeal arches and pouches

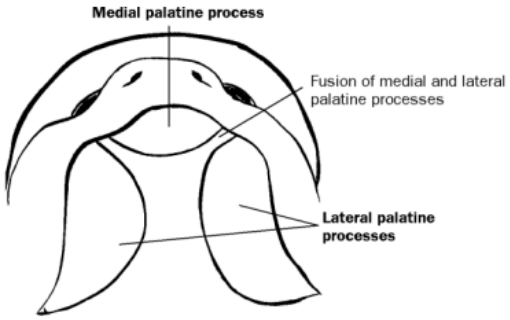


Figure 7 - Development of hard palate

Thyroid Gland

The thyroid gland begins as a downgrowth of the floor of the pharynx called the **thyroid diverticulum**. As it descends down the neck it remains connected to the tongue via the **thyroglossal duct**. In the adult a remnant of this duct persists in the tongue as the **foramen cecum**.

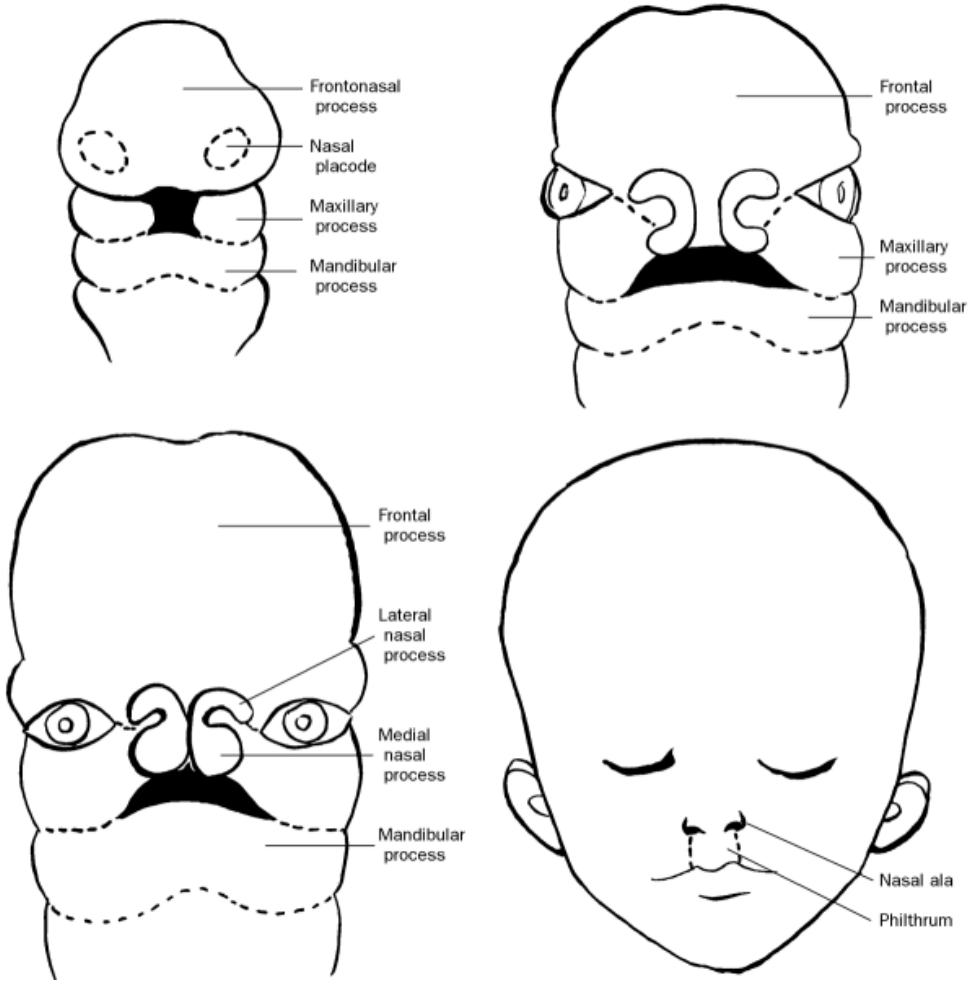


Figure 8 - Development of the face

Primitive Gut Tube

The **primitive gut tube** is derived from the dorsal part of the **yolk sac**, which is incorporated into the body of the embryo during folding of the embryo during the fourth week. The primitive gut tube is divided into three sections.

Table 11 - Sections of the Gut Tube

Section	Blood supply	Adult derivatives
Foregut	Celiac artery	Pharynx, lower respiratory system, esophagus, stomach, proximal half of duodenum, liver and pancreas, biliary apparatus
Midgut	Superior mesenteric artery	Small intestine, distal half of duodenum, cecum and vermiform appendix, ascending colon, most of the transverse colon
Hindgut	Inferior mesenteric artery	Left part of transverse colon, descending colon, sigmoid colon, rectum, superior part of anal canal, epithelium of urinary bladder, most of the urethra

The **epithelium** of and the **parenchyma of glands** associated with the digestive tract (e.g., liver and pancreas) are derived from **endoderm**. The **muscular walls** of the digestive tract (lamina propria,

muscularis mucosae, submucosa, muscularis externa, adventitia and/or serosa) are derived from **splanchnic mesoderm**.
During the **solid stage** of development the endoderm of the gut tube proliferates until the gut is a solid tube. A process of **recanalization** restores the lumen.

Proctodeum and Stomodeum
The proctodeum (anal pit) is the **primordial anus**, and the stomodeum is the **primordial mouth**. In both of these areas ectoderm is in direct contact with endoderm without intervening mesoderm, eventually leading to degeneration of both tissue layers.

Foregut
Esophagus
The **tracheoesophageal septum** divides the foregut into the esophagus and trachea. See the chapter on Respiratory system for more information.

Stomach
The primordium of the **primitive stomach** is visible about the end of the fourth week. It is initially oriented in the median plane and suspended from the dorsal wall of the abdominal cavity by the **dorsal mesentery** or **mesogastrium**. During development the stomach rotates 90° in a clockwise direction along its longitudinal axis, placing the **left vagus nerve** along its anterior side and the **right vagus nerve** along its posterior side. Rotation of the stomach creates the **omental bursa** or **lesser peritoneal sac**.

Duodenum
The duodenum acquires its C-shaped loop as the stomach rotates. Because of its location at the junction of the foregut and the midgut, branches of both the **celiac trunk** and the **superior mesenteric artery** supply the duodenum.

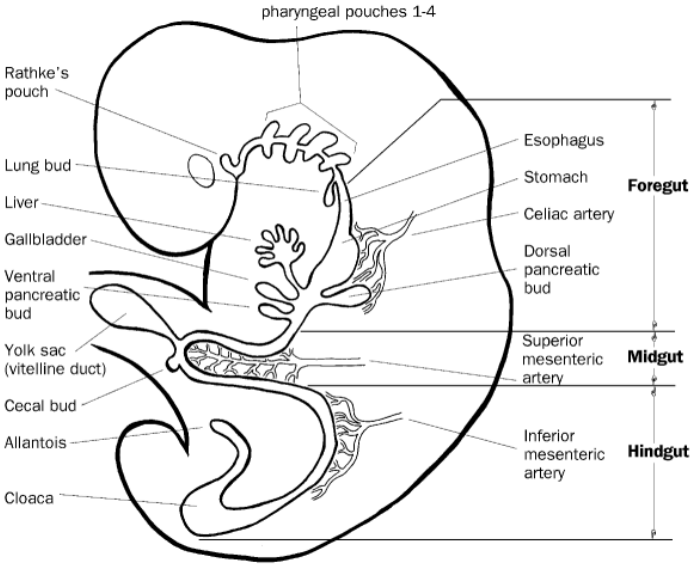


Figure 9 - Primitive Digestive Tract

Pancreas
The pancreas develops from two outgrowths of the endodermal epithelium, the **dorsal pancreatic bud** and the **ventral pancreatic bud**. During rotation of the gut these primordial come together to form a single pancreas. The ventral pancreatic bud forms the uncinate process and part of the head, while the dorsal pancreatic bud forms the remainder of the head, body, and tail of the pancreas. The ducts of the

pancreatic buds join together to form the **main pancreatic duct**, but the proximal part of the duct of the dorsal pancreatic bud may persist as an **accessory pancreatic duct**.

Liver and Biliary Apparatus

The liver develops from endodermal cells that form the **hepatic diverticulum**. The liver grows in close association with the **septum transversum**, which later forms part of the diaphragm. As it grows the hepatic diverticulum divides into a **cranial part**, which forms the **parenchyma** of the liver, and the **caudal part**, which gives rise to the **gallbladder** and **cystic duct**. The **hemopoietic cells**, **Kupffer cells**, and **connective tissue** of the liver are derived from **mesenchyme** in the septum transversum. The embryonic liver is large and fills much of the abdominal cavity during the seventh through ninth weeks of development. Blood formation (hemopoiesis**)** begins in the liver during the sixth week of development, and bile formation begins in the twelfth week.

Spleen

The spleen develops from mesenchymal cells located between layers of the dorsal mesogastrium.

Midgut

The midgut communicates with the yolk sac via the **yolk stalk**. As the midgut forms, it elongates into a U-shaped loop (**midgut loop**) that temporarily projects into the umbilical cord (**physiological umbilical herniation**). The cranial limb of the midgut elongates rapidly during development and forms the **jejunum** and **cranial portion of the ileum**. The caudal limb forms the **cecum**, **appendix**, **caudal portion of the ileum**, **ascending colon**, and **proximal two-thirds of the transverse colon**. The caudal limb is easily recognized during development because of the presence of the **cecal diverticulum**.
The midgut loop rotates **270 counterclockwise** around the **superior mesenteric artery** as it retracts into the abdominal cavity during the **tenth week** of development.

Hindgut

The hindgut is defined to begin where the blood supply changes from the superior mesenteric artery to the **inferior mesenteric artery**, i.e. at the distal third of the transverse colon.

Partitioning of the Cloaca

The cloaca is the endodermally lined cavity at the end of the gut tube. It has a diverticulum into the body stalk called the **allantois**. The **cloacal membrane** separates the cloaca from the proctodeum (**anal pit**). During development a sheet of mesenchyme (**urorectal septum**) develops to divide the cloaca into a ventral (**urogenital sinus**) and a dorsal portion (**anorectal canal**). By week seven the urorectal septum reaches the cloacal membrane, dividing it into ventral (**urogenital membrane**) and dorsal (**anal membrane**) portions.

Anal Canal

The epithelium of the superior two-thirds of the anal canal is derived from the endodermal hindgut; the inferior one-third develops from the ectodermal proctodeum. The junction of these two epithelia is indicated by the **pectinate line**, which also indicates the approximate former site of the **anal membrane** that normally ruptures during the **eighth week** of development.

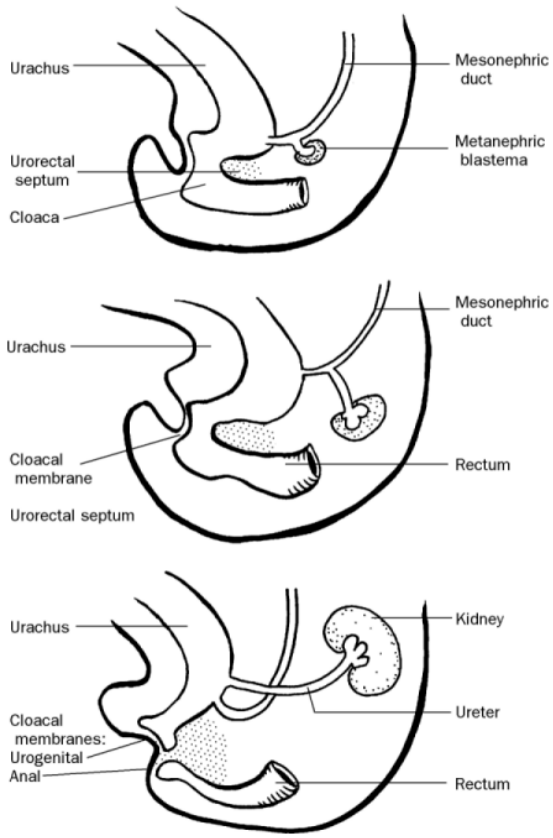


Figure 10 - Partitioning of the common cloaca

Clinical Correlations

Esophageal Atresia

Esophageal atresia usually results from abnormal division of the tracheoesophageal septum. The fetus is unable to swallow and this results in **polyhydramnios** (excessive amount of amniotic fluid) because amniotic fluid cannot pass into the intestines for return to the maternal circulation.

Congenital Hypertrophic Pyloric Stenosis

Overgrowth of the longitudinal muscle fibers of the pylorus creates a marked thickening of the pyloric region of the stomach. The resulting stenosis (Gk. severe narrowing) of the pyloric canal obstructs passage of food into the duodenum, and as a result after feeding the infant expels the contents of the stomach with considerable force (projectile vomiting). This condition affects approximately 1/150 male infants, but only 1/750 female infants.

Annular Pancreas

The ventral and dorsal pancreatic buds form a ring around the duodenum, thereby obstructing it.

Ileal Diverticulum (Meckel's Diverticulum)

A remnant of the proximal part of the yolk stalk that fails to degenerate during the early fetal period results in a finger-like blind pouch that projects from the ileum. While this condition occurs in about 1/50 people, it is usually asymptomic and only occasionally leads to abdominal pain and/or rectal bleeding.

Omphalocele

The midgut fails to retract into the abdominal cavity. At birth, coils of intestine covered with only a **transparent sac of amnion** protrude from the umbilicus. Ugh.

Malrotations of the Midgut

The midgut does not rotate normally as it retracts into the abdominal cavity. This usually presents as symptoms of intestinal obstruction shortly after birth. Malrotation also predisposes the infant to a **volvulus of the midgut**, wherein the intestines bind and twist around a short mesentery. Volvulus usually interferes with the blood supply to a section of the intestines, and can lead to necrosis and gangrene.

Sub-hepatic Cecum and Appendix

The cecum and appendix adhere to the inferior surface of the liver during the fetal period, and are carried upwards with it, resulting in an abnormal anatomical position that may create difficulties in diagnosing appendicitis.

Stenosis and Atresia of the Small Intestine

Failure of recanalization of ileum during the solid stage of development leads to stenosis (narrowing) or atresia (complete obstruction) of the intestinal lumen. Some stenoses and atresias may be caused by an infarction of the fetal bowel owing to impairment of its blood supply (cf. volvulus).

Congenital Aganglionic Megacolon (Hirschsprung's disease)

This results from the failure of neural crest cells to migrate and form the myenteric plexus in the sigmoid colon and rectum. The resulting lack of innervation results in loss of peristalsis, fecal retention, and abdominal distention.

Anorectal Agenesis

Abnormal formation of the urorectal septum causes the rectum to end as a blind sac above the puborectalis muscle.

Anal Agenesis

Abnormal formation of the urorectal septum causes the rectum to end as a blind sac below the puborectalis muscle.

Imperforate Anus

The anal membrane fails to break down before birth. The anus must be reconstructed surgically, with severity depending on the thickness of the intervening tissue.

Lower Respiratory System

The primordium of the lower respiratory system develops in about the fourth week. The **laryngotracheal diverticulum** arises from endoderm on the ventral wall of the foregut. **Tracheoesophageal folds** develop on either side and join to form a **tracheoesophageal septum** that separates it from the rest of the foregut. This divides the foregut into the **laryngotracheal tube** (ventral) and the **esophagus** (dorsal). The caudal end of the laryngotracheal diverticulum enlarges to form the **lung bud**, which is surrounded by **splanchnic mesenchyme**.

Larynx

The opening of the laryngotracheal tube becomes the **inlet of the larynx**. **The laryngeal cartilages** are derived from the **fourth and sixth pharyngeal arches**.

Trachea

The **epithelium and glands** of the trachea develop from **the** endoderm **of the laryngotracheal tube**. The **cartilage, connective tissue, and smooth muscle** are derived from the surrounding **splanchnic mesenchyme**.

Bronchi

At the end of the fourth week the lung bud divides into two **bronchial buds**, which enlarge to form the **primary bronchi**. The **right bronchus** is **larger** and more **vertically oriented** than the left one, and this relationship persists throughout life. In the fifth week, each bronchial bud divides into **secondary bronchi**. In the eighth week the secondary bronchi divide to form the **segmental bronchi** (tertiary bronchi), ten in the right lung and eight in the left. Each segmental bronchus becomes a bronchopulmonary segment (segment in a lung). The **smooth muscle**, **connective tissue**, and **cartilaginous plates** in the bronchi are derived from **splanchnic mesenchyme**.

Table 14 - Stages of Lung Development

Time period	Stage	Notes
Weeks 5 – 17	Pseudoglandular	Developing lungs resemble an exocrine gland. Respiration is not possible. **Fetuses born during this period cannot survive**.
Weeks 16 – 25	Canalicular	Terminal bronchioles divide and primitive alveolar sacs (**terminal sacs**) develop. Some respiration may be possible towards the end of this stage. **Fetuses born towards the end of this period (weeks 22-25) can survive if given intensive care** but often die anyway.
Week 24 – birth	Terminal sac	Many more alveoli develop, and the epithelium lining the terminal sacs become thin enough to allow respiration. Type I and Type II pneumocytes develop. Type II pneumocytes begin producing **pulmonary surfactant**, which counteracts surface tension and facilitates expansion of the terminal sacs at birth**. Fetuses born after 24 weeks may survive**, and those born after 32 weeks have a good chance of survival.
Birth – year 8	Alveolar	Respiratory bronchioles, terminals, alveolar ducts continue to increase in number

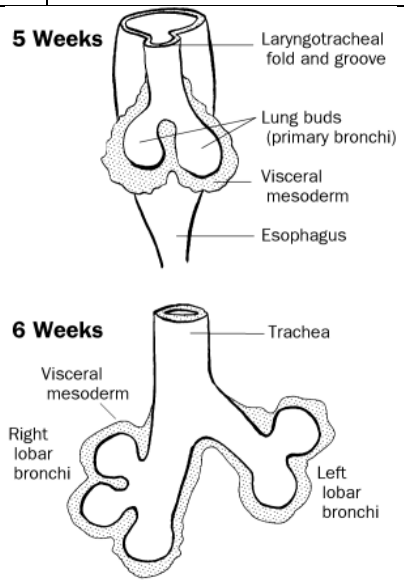


Figure 13 - Development of Lungs

Clinical Correlations

Tracheoesophageal Fistula

An abnormal communication between the trachea and esophagus due to incomplete separation of the trachea and esophagus during the fourth week of development. It is commonly associated with

esophageal atresia. Newborn infants with these malformations cough and choke during eating due to the aspiration of food and saliva into the lungs.

Respiratory Distress Syndrome

Respiratory Distress Syndrome is common in premature infants and is due to a **deficiency of surfactant**. It is commonly associated with **hyaline membrane disease** in which the alveolar surfaces of the lungs are coated with a glassy hyaline membrane. Treatment with **thyroxin** and **cortisol** can increase production of surfactant.

Pulmonary Hypoplasia

Pulmonary hypoplasia results when lungs are compressed by abnormally positioned abdominal viscera and cannot develop normally or expand at birth. It is commonly caused by congenital **posterolateral diaphragmatic hernia**.

Urogenital System

The urogenital system arises during the fourth week of development from **urogenital ridges** in the **intermediate mesoderm** on each side of the primitive aorta. The **nephrogenic ridge** is the part of the urogenital ridge that forms the urinary system. Three sets of kidneys develop sequentially in the embryo: The **pronephros** is rudimentary and nonfunctional, **and regresses completely**. The **mesonephros** is functional for only a short period of time, and remains as the **mesonephric (Wolffian**) **duct**. The **metanephros** remains as the permanent adult kidney. It develops from the **uteric bud**, an outgrowth of the mesonephric duct, and the **metanephric mesoderm**, derived from the caudal part of the nephrogenic ridge.

Urine excreted into the amniotic cavity by the fetus forms a major component of the amniotic fluid. Urine formation begins towards the end of the first trimester (weeks 11 to 12) and continues throughout fetal life.

The **kidneys develop in the pelvis and ascend** during development to their adult anatomical location at **T12-L3**. This normally happens by the **ninth week**.

Table 12 - Adult Derivatives of Embryonic Kidney Structures

Embryonic Structure	**Adult Derivative**
Ureteric bud (metanephric diverticulum)	Ureter Renal pelvis Major and minor calyces Collecting tubules
Metanephric mesoderm	Renal glomerulus + capillaries Bowman's capsule Proximal convoluted tubule Loop of Henle Distal convoluted tubule

Suprarenal Gland

The **adrenal medulla** forms from neural crest cells that migrate into the fetal cortex and differentiate into **chromaffin cells**.

Urinary Bladder

The **urinary bladder** develops from the upper end of the **urogenital sinus**, which is continuous with the allantois. It is lined with **endoderm**. The lower ends of the metanephric ducts are incorporated into the wall of the urogenital sinus and form the **trigone of the bladder**. The connective tissue and smooth muscle surrounding the bladder are derived from adjacent **splanchnic mesoderm**.

The **allantois** degenerates and remains in the adult as a fibrous cord called the **urachus (median umbilical ligament)**.

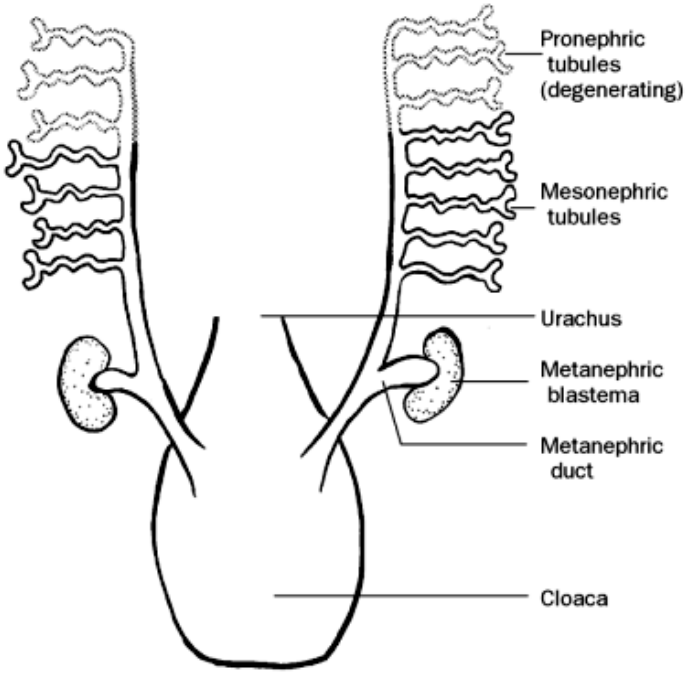


Figure 11 - Development of the kidneys

Clinical Correlations

Renal agenesis

Absence of a kidney results when the ureteric bud fails to develop or regresses after development. If both kidneys are absent (**bilateral renal agenesis**) the fetus cannot urinate and amniotic fluid is deficient (< 400ml) resulting in **oligohydramnios** and characteristic physical deformations known as **Potter facies** (flattened nose, low-set ears, thickened, tapering fingers).

Congenital Polycystic Disease of the Kidneys

An autosomal recessive condition manifest by the presence of many heterogeneous cysts within the parenchyma of the kidney. The cause and pathogenesis is unknown.

Horseshoe Kidney

Horseshoe kidney occurs when the inferior poles of the kidneys fuse together. The combined kidney is not able to ascend to its adult physiological location because it gets "hung up" on the inferior mesenteric artery.

Pelvic Kidney

A **pelvic kidney** is one that has failed to migrate to its adult anatomical location. In **crossed ectopia** one kidney and its associated ureter migrate to the opposite side of the body.

Urachial Fistula

If the lumen of the **allantois persists** as the urachus forms it may give rise to an abnormal communication between the urinary bladder and the umbilicus known as an **urachal fistula**. Often with this condition urine will dribble from the umbilicus when the baby cries. A blind-ending communication that will not drain urine is known as an **urachal sinus**.

Determination of Gender

Although genetic sex (XX or XY) is determined at fertilization, the embryo's gender is not distinguishable for the first six weeks of development; this is known as the **indifferent period of development**. Characteristics of either male or female genitalia can often be recognized by week twelve of development.

Development of External Genitalia

In both sexes about the fourth week of development an indifferent **genital tubercle** develops near the cloaca and elongates to form a **phallus**. In a male embryo, androgens secreted by the testes cause the phallus to elongate into the **penis** and the **urogenital folds** to fuse and form the **spongy urethra**. Without influence of androgens, the phallus becomes the **clitoris**, the **urogenital folds** become the **labia minora**, and the **labioscrotal swellings** become the **labia majora**. The external genital organs are not fully differentiated until about the **twelfth week** of development.

Development of Genital Ducts

During indifferent development both pairs of genital ducts are present. In **female** embryos the **paramesonephric ducts** (**müllerian ducts**) develop into most of the female genital tract, including the **uterine tubes**, **uterus**, and part of the **vaginal canal**. In **male** embryos the testes secrete **müllerian inhibiting substance**, which suppresses development of the paramesonephric ducts. Instead the **mesonephric ducts** develops into the **epididymis**, **ductus deferens**, and **ejaculatory duct**.

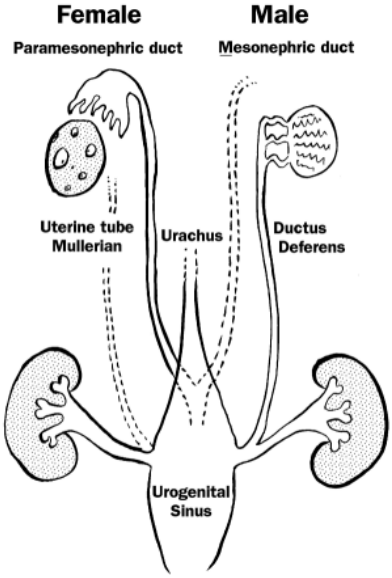


Figure 1 - Adult persistence of embryonic ducts in the genitourinary system

Descent of the Ovaries and Testes

The ovaries and testes develop in the abdomen and descend to their adult anatomical positions before birth. In the male the **testes descend** from the abdomen into the scrotum about the **twenty-eighth** week of development.

Clinical Correlations

Hypospadias
Incomplete fusion of the urogenital folds creates abnormal openings of the urethra on the ventral aspect of the penis. This malformation occurs in about 1/300 infants.

Malformations of the Uterus and Vagina
If the two paramesonephric ducts fail to fuse correctly it can result in duplication of the uterus and vagina (**double uterus and double vagina**). If one paramesonephric duct fails to develop it results in formation of a single uterine tube and single horn of the uterus (**unicornuate uterus**).

Cyrptorchidism
Failure of the testes to descend into the scrotum (**cryptorchidism**) is the most common malformation of the male genital system, resulting in infertility and an increased risk of testicular cancer. The testes may remain anywhere between the abdomen and the scrotum.

Intersexuality
Rare **true hermaphrodites** have both ovarian and testicular tissues, usually possessing a **46,XX** karyotype. The internal and external and external genitalia are variable. **Female pseudohermaphrodites** are more common, possessing a **46, XX** karyotype, and typically result from exposure to excess androgens during embryologic development (as in **congenital virilizing adrenal hyperplasia)**. **Male pseudohermaphrodites** have testes and a **46, XY** karyotype. This condition results from an inadequate production of androgens by the testes, or when embryonic genital tissues lack a specific receptor needed to respond to normal levels of the hormone.

Congenital Inguinal Hernia
A large patency of the tunica vaginalis can allow a loop of intestine to herniate into the scrotum. This must typically be corrected surgically.

Development of Heart
Two **endocardial heart tubes** arise from **cardiogenic mesoderm**. As lateral folding occurs, these fuse to form the **primitive heart tube**, which develops into the **endocardium**. The **myocardium** and **epicardium** develop from **mesoderm** surrounding the primitive heart tube.
Several contractions and dilations soon appear in the heart tube, all of which have adult remnants.

Table 13 - Fates of Embryonic Dilatations of the Primitive Heart Tube

Embryonic Dilatation	Adult Structure
Sinus venosus	Smooth part of right atrium (sinus venarum), coronary sinus, oblique vein of left atrium
Primitive atrium	Trabeculated parts of right and left atria
Primitive ventricle	Trabeculated parts of right and left ventricles
Bulbis cordis	Smooth part of right ventricle (conus arteriosus), smooth part of left ventricle (aortic vestibule)

Truncus arteriosus	Aorta, pulmonary trunk

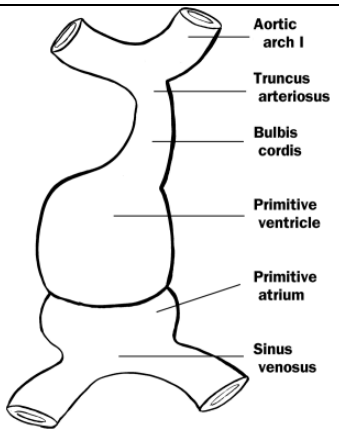


Figure 11 - Primitive heart

Development of Blood Vessels

Blood vessel formation (**angiogenesis**) starts at the beginning of the third week. Blood vessels first start to develop in the extraembryonic mesoderm of the yolk sac, connecting stalk, and chorion. Blood vessels begin to develop in the embryo about two days later.

Production of Blood

Production of blood (**hemopoiesis** or **hematopoiesis**) begins first in the **yolk sac wall** about the third week of development. **Erythrocytes produced in the yolk sac have nuclei**. Blood formation does not begin inside the embryo until about the **fifth week**. **Erythrocytes produced in the embryo do not have nuclei** (eunucleated). Hematopoiesis inside in the embryo occurs first in the **liver**, then later in the **spleen**, **thymus**, and **bone marrow**.

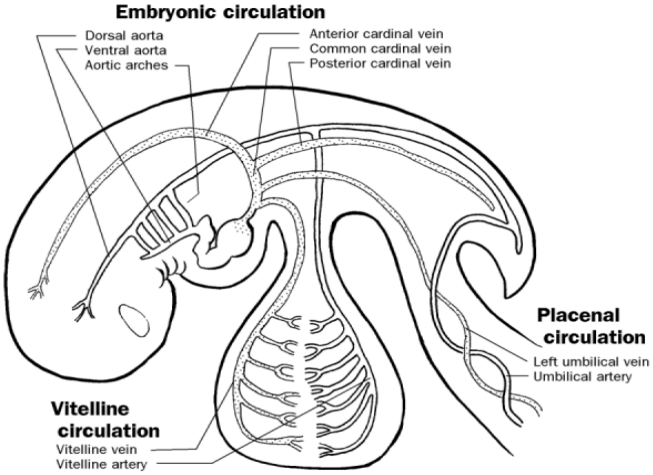


Figure 12 - The three embryonic circulations

General

The fine hair on a newborn infant is known as **lanugo**. It helps to anchor **vernix caseosa** ("cheese-like varnish"), a waxy substance that protects the fetus from maceration by the amniotic fluid.

Circulatory Changes at Birth

At birth, placental blood flow ceases and lung respiration begins. The sudden drop in right atrial pressure pushes the septum primum against the septum secundum, closing the **foramen ovale**. The **ductus arteriosus** begins to close almost immediately, and may be kept open by the administration of

prostaglandins. Other embryonic circulatory vessels are slowly obliterated and remain in the adult only as fibrous remnants.

Table 17 - Adult Remnants of Fetal Circulatory Structures

Fetal Structure	**Adult Remnant**
Foramen ovale	*Fossa ovalis* of the heart
Ductus arteriosus	*Ligamentum arteriosum*
Left umbilical vein	
Extra-hepatic portion	*Ligamentum teres hepatis*
Intra-hepatic portion (ductus venosus)	*Ligamentum venosum*
Left and right umbilical arteries	
Proximal portions	Umbilical branches of internal iliac arteries
Distal portions	Medial umbilical ligaments

Clinical Correlations

Patent Foramen Ovale

Failure of the foramen ovale to close at birth, e.g., due to faulty development of the septum primum and/or septum secundum. This condition is usually physiologically insignificant.

Patent Ductus Arteriosus

Failure of the ductus arteriosus to close after birth. Patients with some heart anomalies can survive only if they have a patent ductus arteriosus. Administration of prostaglandins can delay the closure of the ductus arteriosus. Conversely, drugs that inhibit prostaglandin synthesis (e.g. with indomethacin) can sometimes be used to close the ductus arteriosus without surgery.