

8. Development of digestive system II. Rotation of intestine. Liver, pancreas, spleen. Development of respiratory passages and lung.

Duodenum

- originates partially from the terminal part of the foregut, which is proximal to the liver bud (supplied by the superior and inferior pancreaticoduodenal arteries from the gastroduodenal artery from the coeliac trunk)
- originates also partially from the cephalic part of the midgut, which is distal to the liver bud (supplied by the inferior pancreaticoduodenal art. from the superior mesenteric artery)
- as the stomach rotates to the right → the duodenum takes on the form of a “C”-shaped loop
- the dorsal mesoduodenum fuses with the adjacent dorsal parietal peritoneum → most of the duodenum and the head of the pancreas becomes fixed in a retroperitoneal position
- in month 2, the lumen is obliterated by proliferating enterocytes; later on, the lumen is recanalized again

Liver

- the liver primordium appears in the middle of the week 3 from the entoderm at the distal end of the foregut
- this liver bud (hepatic diverticulum) penetrates the mesodermal mesenchyme of the ventral mesentery, named the septum transversum
- the liver bud proliferates and forms a lumen, thus forming the bile duct; a small ventral outgrowth gives rise to the cystic duct and to the gall bladder
- the common bile duct branches to the right and left hepatic ducts; their proliferation gives rise to two hepatic lobes
- the liver cords branch from the hepatic ducts; the epithelial cells differentiate into the parenchyma (liver cells) and lining of the biliary ducts
- the epithelial liver cords grow into the vitelline and umbilical veins; these veins form the hepatic sinusoids
- the mesoderm of the septum transversum (ventral mesentery) differentiates into
 - hepatic connective tissue cells (hematopoietic cells, Kupffer cells and connective tissue stromal cells)
 - hepatic fibrous capsule,
 - and forms the falciform ligament and the lesser omentum
- mesoderm on the surface of liver differentiates into visceral peritoneum
- only the cranial surface of the liver remains in contact with the septum transversum, the portion of which will form the central tendon of the diaphragm; the surface of liver that is in contact with the future diaphragm is not covered by peritoneum and it is named the bare area of the liver
- the bile is formed in the liver since week 12
- because of the positional shift and rotation of duodenum, the bile duct shifts from anterior position to a posterior one and then the bile ducts passed behind the duodenum
- since week 6, the hematopoiesis starts in the liver; it becomes fully developed since week 10, becoming the major site of fetal hematopoiesis; since month 8, the hepatic hematopoiesis becomes reduced as this process is transferred to the bone marrow cavity

Pancreas

- two buds, dorsal and ventral, originate from the entodermal lining of the duodenum; later on, the parenchyma and the duct system of these two pancreatic primordia fuse
 - **the dorsal pancreatic bud** is bigger and it grown within the dorsal mesentery (opposite to the liver bud)
 - it forms the superior part of the head of the pancreas, the body, and the tail of the pancreas
 - from its original duct, the distal part persists and connects with the duct of the ventral pancreas
 - the proximal part of the duct is either obliterated or may persist as the accessory pancreatic duct (of Santorini), which enters the duodenum at the site of the minor duodenal papilla
 - **the ventral pancreatic bud** originates as a branch of the liver bud
 - when duodenum rotates to the right, the ventral bud migrates dorsally and comes to lie below and behind the dorsal bud
 - it forms the uncinated process and the inferior part of the head of the pancreas
 - its duct form the main pancreatic duct (of Wirsung), which enters the duodenum at the site of the major duodenal papilla → the connection and branching pattern of the pancreatic and the choledochus duct is highly variable
- in the month 3, some entodermal pancreatic cells differentiate into endocrine islets of Langerhans; insulin secretion in β -cells begins at month 5

Abnormalities of liver and pancreas

- aberrant branching of biliary passages (may be asymptomatic)
- accessory hepatic duct
- atresia of extrahepatic and intrahepatic biliary passages → the bile causes damage to the hepatocytes
- abnormal rotation of the ventral pancreas → the duodenum is surrounded by a ring of pancreatic tissue, which is named the annular pancreas; this may cause constriction or obstruction of the duodenum
- ectopic pancreatic tissue (in stomach, duodenum, jejunum, ileum, or Meckel's diverticle)

Midgut

- in week 5 it is suspended from the dorsal abdominal wall by a short mesentery
- the midgut is supplied by the superior mesenteric artery, which is also the axis of midgut rotation
- it elongates rapidly → formation of the **primary intestinal loop**
 - first, it communicates with the yolk sac via the vitelline duct (yolk stalk)
 - the cephalic limb of the loop develops into → distal part of the duodenum (distal to the liver bud), the jejunum, and part of the ileum
 - the caudal limb of the loop develops into → lower portion of the ileum, the caecum, the appendix, the ascending colon, and the proximal 2/3 of the transverse colon
- **physiological umbilical herniation of the midgut loops**
 - between weeks 6-10, the elongated midgut loops enter the extraembryonic cavity in the umbilical cord as the abdominal cavity is too small to contain all the loops

- in week 10 the loops return to the abdominal cavity (retraction of herniated loops); first, the proximal jejunum reenters, followed by ileum; finally, the caecal bud is the last part of the gut to reenter the abdominal cavity
- the midgut loop rotates 270° counterclockwise around the superior mesenteric artery (90° rotation during the herniation and 180° after reposition)
- during the rotation, the caecum migrates cranially and pulls the ascending and the transverse colon; then the caecum descends to the iliac fossa (→ this may result in various positions of the appendix, which develops during the descensus); the left and the right colic flexures originate
- mesenteries of the intestinal loops
 - the dorsal mesentery twists around the superior mesenteric artery
 - the mesentery (mesocolon) of the ascending and the descending colon is pressed against the peritoneum of the posterior abdominal wall; these layers fuse, thus anchoring the ascending and descending colons in a retroperitoneal position
 - the transverse mesocolon maintains its mobility and fuses with the two layers of the greater omentum
 - the roots of the mesenteries of jejunum and ileum join the dorsal abdominal wall along a line connecting the duodenojejunal flexure with the ileocaecal junction

Hindgut

- gives rise to the distal third of the transverse colon (supplied by the left colic artery), the descending colon, the sigmoid, the rectum, and the upper part of the anal canal
- its epithelium forms also the internal lining of the bladder and urethra
- the terminal part of the hindgut enters the **cloaca**; the parts of the cloaca are as follows:
 - dorsally, there is the terminal part of the hindgut
 - ventrally, there is the urogenital sinus
 - mesodermal layer named the urorectal septum separated the dorsal hindgut from the ventral urogenital sinus; the urorectal septum comes close to the cloacal membrane and forms the perineum (its central tendinous part)
 - until week 8, the cloaca is closed with the cloacal membrane, which temporarily separates the entoderm of the hindgut from the ectodermal proctodeum
 - the cloacal membrane ruptures, creating dorsally the anal opening for the hindgut and ventrally the opening for the urogenital sinus; between these two openings, the perineum originates
 - the anal canal
 - the ectoderm in the region of proctodeum proliferates and invaginates to create the anal pit (this region is supplied by the inferior rectal arteries, branches of the internal pudendal arteries)
 - the entoderm of the terminal hindgut forms the cranial part of the anal canal (supplied by the superior rectal arteries, branches of the inferior mesenteric artery)
 - the epithelial junction between the entodermal (simple columnar) and ectodermal (stratified squamous non-keratinized) regions of the anal canal named the pectinate line, just below the anal columns

Body cavities, body wall and the diaphragm

- the intraembryonic coelom cavity is limited dorsally and laterally by the somatopleuric mesoderm; during the closure of the body wall, the somatopleura fuses with the ventral splanchnopleuric mesoderm
 - the somatopleuric mesothelium → gives rise to the parietal layer of the serous membranes
 - the splanchnopleuric mesothelium → gives rise to the visceral layer of the serosa
- the coelomic cavity is lined with the mesodermal serous membrane with the mesothelial epithelium on its surface
 - it is partitioned to the pleural cavity, the peritoneal cavity, and the pericardial cavity
 - before complete separation of these serous cavities, the pleuropericardial canals are connecting the pleural with the pericardial cavities; the canals become narrowed by expanding pleuropericardial folds
 - the diaphragm separates the pleural cavity from the peritoneal cavity
- the diaphragm develops from several structures:
 - the septum transversum, which is a mesodermal plate forming the central tendon of the diaphragm;
 - the two pleuroperitoneal membranes, which are folds growing from dorsolateral walls of the body wall in the ventral and medial direction, thus closing the pleuroperitoneal canals
 - muscular components from ventrolateral cervical myotomes, these retain the innervation from C3-C5 spinal cord segments
 - the mesentery of the esophagus, which develops in the right and the left crura of the diaphragm

Spleen

- several mesodermal splenic islets fuse within the dorsal mesogastrium
- the spleen is bulging to the left side with the dorsal mesogastrium
- it becomes infiltrated with hemopoietic cells, thus contributing to the prenatal hepatolienal hemopoiesis
- separate lineal islets may persist as aberrant accessory splenic tissue within the gastroduodenal ligament, pancreas, etc.

Abnormalities of midgut, abdominal wall and mesenteries

- the vitelline duct partially persists in approx. 3% of people, forming an outpocketing of the ileum, named ileal (Meckel's) diverticulum; in the adult, it is found approx. 40-60 cm proximally to the ileocaecal valve; the diverticle may contain cysts or it may connect the lumen of the ileum with the umbilicus, thus forming a vitelline (faecal) fistula
- aberrant rotation (malrotation) of the intestinal loop; incomplete rotation; reversed rotation; duplication of intestinal loops
- atresias (the lumen is lacking) or stenoses (narrowing of the lumen); usually caused by insufficient vascular supply
- persistence of a portion of the mesocolon gives rise to the mobile caecum
- omphalocele involves herniation of abdominal viscera (intestine, stomach, spleen...) through an enlarged umbilical ring; the viscera fail to return into the abdominal cavity; the viscera are covered by amnion

- gastroschisis (laparoschisis) is a protrusion of abdominal viscera through a body wall defect into the amniotic cavity; the intestinal loops are not covered by amnion; the defects is due to abnormal closure of the body wall, mostly right to the umbilicus
- when pleuroperitoneal folds fail to close the pleuroperitoneal canals, the peritoneal and pleural cavities communicate, which results in congenital diaphragmatic herniation of abdominal viscera into pleural cavity; the lungs may be compressed by this herniation

Abnormalities of hindgut

- aberrant or incomplete division of cloaca with the urorectal septum → rectourethral and rectovaginal fistula
- atresia of rectum or anus is caused by persisting cloacal membrane
- congenital megacolon (Hirschprung disease) results from a failure of formation of parasympathetic ganglia in the wall of colon and rectum (failure of neural crest migration); due to insufficient peristalsis, the colon is dilated above the affected region, which lacks innervation and has a small diameter

Respiratory system

- at the end of week 4, the respiratory diverticulum (lung bud, laryngotracheal diverticulum) grows ventrally from the foregut; the epithelium of the respiratory system including and distal from the larynx has entodermal origin
- the lung bud expands caudally; two longitudinal tracheoesophageal ridges separate it from the foregut
- the respiratory primordium maintains its communication with the pharynx through the laryngeal orifice
- the connective tissue of the bronchi and longs originate from the splanchnopleuric mesenchyme of the foregut
- the lung bud forms the traches and two bronchial buds:
 - in week 5, right and left main bronchi are formed
 - with subsequent growth, the secondary lobar bronchi form (2 on the left, 3 on the right side); branching of tertiary bronchi results in formation of segmental bronchi (8 in the left lung and 10 in the right lung)
 - by the end of the month 6, approx. 17 generations of subdivisions of the intrapulmonary bronchial tree have formed
 - an additional 6 divisions form during postnatal life
 - stages in development and maturation of the lungs
 - pseudoglandular period (week 5-16), terminal bronchioles are formed; no respiratory bronchioles or alveoli are present
 - canicular period (week 16-26), each terminal bronchiole divides into respiratory bronchioles, which divide into alveolar ducts
 - terminal sac period (week 26 to birth), terminal sacs (= primitive alveoli) are formed; the epithelium of the alveoli becomes thinner and capillaries establish close contact with the wall of the alveoli
 - alveolar period (from 8 months to childhood), mature alveoli have well-developed contacts between flattened alveolar epithelium (type I pneumocytes) and capillary endothelial cells; the definitive alveolocapillary membrane (blood-air barrier) is formed
 - since month 6, type II alveolar pneumocytes differentiate and produce surfactant

- the surfactant is a phospholipid-rich fluid capable of lowering surface tension at the air-alveolar interface, thus lowering the mechanical work necessary for expansion of the alveolar surface during inspiration and prevents the alveoli from collapse during expiration
- as the composition of the surfactant matures, the ratio between the lecithin and sphingomyelin may be measured from an amniotic fluid sample; this can be used for estimating the maturation of the fetal lungs
- production of lecithin increases after week 32; the surfactant becomes more effective
- mothers may be treated with glucocorticoids shortly before expected premature birth to accelerate surfactant maturation and to stimulate its production; this may decrease the risk of respiratory distress syndrome
 - fully differentiated alveoli are completed after birth
- the mesenchyme of the pharyngeal arches form the cartilages and muscles of the larynx
- the larynx is innervated by the vagus nerve: the superior laryngeal nerve (supplies the muscles of the 4th pharyngeal arch, the cricothyroid muscle) and the recurrent laryngeal nerve (supplies the muscles originating from the 6th pharyngeal arch, i.e., the intrinsic laryngeal muscles)
- fetal breathing movements begin before birth → the amniotic fluid is aspirated; when breathing begins at birth, most of the lung fluid is rapidly resorbed by the lung blood and lymph microcirculation or it is expelled from the lungs
- with the onset of respiration, the lungs expand and the vascular resistance of the pulmonary circulation drops → the blood from the pulmonary trunk flows into the lungs → more vein returns from the lungs via the pulmonary veins into the left atrium → the foramen ovale is closed
- new alveoli are formed and grow during the first 10 years

Abnormal development of respiratory system

- abnormal partitioning of the esophagus and trachea by the tracheoesophageal septum results in esophageal atresia
 - this may be connected with the tracheoesophageal fistulas connecting the oesophagus with the trachea; a complication of this condition is polyhydramnion, as the abdominal fluid may not pass to the stomach; after birth, aspiration of milk into lungs may cause pneumonia
 - in the most frequent type, the upper part of the oesophagus ends blindly and the lower part of oesophagus is connected with the trachea via a fistula
 - this condition is frequently linked also with heart defects
- abnormal branching of the bronchial tree results in aberrant or ectopic lung lobes
- dilation of terminal or larger bronchi results into congenital cysts of the lung
- insufficient production or maturation of the surfactant results is frequent in premature infants → respiratory distress syndrome develops: alveoli collapse during expiration; the partially collapsed alveoli may contain a fluid with high protein content, a condition named hyaline membrane disease; it prevents the transport of the respiratory gases
- mothers may be treated with glucocorticoids shortly before expected premature birth to accelerate surfactant maturation and to stimulate its production