

# INTRODUCTION TO EMBRYOLOGY II

## Embryonic Cephalocaudal and Lateral Flexion/Folding

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### Summary:

In this lecture we shall concentrate on those events which transform the trilaminar embryo into a “tube within a tube”, segregating the embryo from extraembryonic tissue except at the umbilicus. These processes will also rotate the developing heart tube into its thoracic position. Finally, we shall examine how the coelom is divided into the pleural, peritoneal and pericardial cavities.

### Learning objectives:

1. To understand how the embryo is segregated from the extra-embryonic tissues with the exception of the umbilical cord.
2. To understand the process whereby the gut tube is formed and is lined with endoderm.
3. To understand the events that result in the incorporation of the extra-embryonic coelom into the embryo, thereby forming the peritoneal, pericardial and pleural cavities.
4. To understand the role of cranial-caudal flexion in the repositioning of the buccopharyngeal membrane (future opening of the mouth), heart tubes, primitive pericardial cavity and a wedge of mesoderm (septum transversum) which will initiate diaphragm formation. At the same time the cloacal membrane (future opening of gut and urinary tract) is also brought into a ventral position.
5. To understand how the diaphragm is formed.

### Glossary:

**Allantois** - hindgut diverticulum lined with endoderm. It is carried ventrally at tail fold and fuses with the umbilical cord.

**Amniotic cavity** - fluid filled space initially between the amniotic membrane and epiblast which, following folding, surrounds the embryo/fetus.

**Amniotic membrane** - derived from the epiblast by delamination (see Lecture 1).

**Buccopharyngeal membrane** - site of future opening of the mouth.

**Cardiogenic area** - region of splanchnopleure rostral to the buccopharyngeal membrane, where heart differentiation is initiated.

**Dorsal mesentery** - a thin bilayered mesoderm derivative from which the abdominal viscera are suspended. The organs that remain suspended are termed intraperitoneal. Other organs are not suspended by this mesentery are separated from the coelom by a serous membrane. These are retroperitoneal (e.g. kidney). Some organs are secondarily retroperitoneal (ascending and descending colon).

**Embryonic coelom** - originates from the extra-embryonic coelom. It is incorporated into the embryo as the lateral plate mesoderm divides into somatopleure and splanchnopleure. Eventually the space is divided into peritoneal, pleural and pericardial cavities.

**Extra-embryonic coelom (also called chorionic cavity)** - space that is bounded by extra-embryonic mesoderm.

**Head fold** - (also called cranial or mesencephalic flexure) bending of cranial aspect of the embryo ventrally, most likely due to the rapid growth of the forebrain and the relative stiffness of the notochord. This process brings the mouth and heart into their ventral positions.

**Lateral folding (or flexion)** - the lateral edges of the embryonic disc flex sharply ventral. The edges of each germ layer make contact at head and tail regions and zipper toward the umbilicus. The ectoderm now covers the entire body surface except at the umbilical region where the connecting stalk and yolk sac merge.

**Pericardioperitoneal canals**- openings between the primitive pericardial and peritoneal cavities.

**Pleuropericardial folds** - flaps of body wall at the level of the primitive pericardial cavity. They grow medially and fuse with the ventral surface of the foregut mesoderm. These folds subdivide the primitive pericardial cavity into the definitive pericardial and two pleural cavities. The pleural cavities remain open to the peritoneal cavity via what are still called the pericardioperitoneal canals.

**Pleuroperitoneal membranes** - transverse flaps of lateral plate mesoderm grow ventral to fuse with the septum transversum, closing the pericardioperitoneal canals. If these canals do not close, herniation of gut structures can occur into the pleural cavity.

**Septum transversum** -thickened bar of lateral plate mesoderm between the cardiogenic area and the cranial margin of the embryonic disc. It is brought into the thorax when the head folds to lie below the heart. It is the first component of the diaphragm dividing the pleural/pericardial space (thoracic cavity) from the peritoneal (abdominal cavity).

**Somatopleure** - lateral plate mesoderm of the body wall.

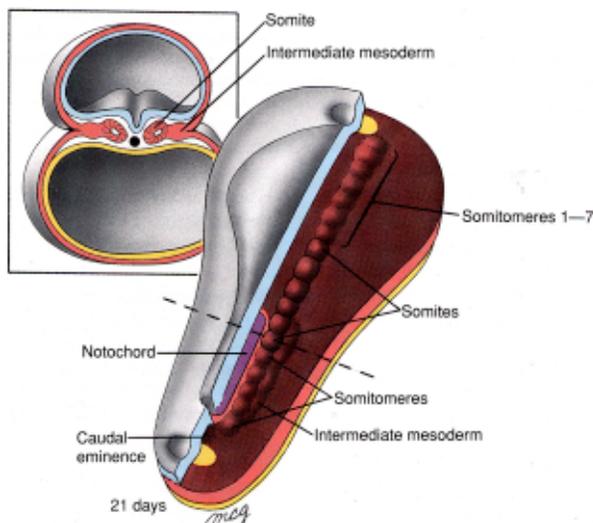
**Splanchnopleure** - lateral plate mesoderm associated with the gut tube and the heart (cardiac muscle).

**Tail (or caudal) fold** - bending of the caudal aspect of embryo ventrally to reposition the cloaca and allantois. The cloaca will be sub-divided into the urinary and anal openings.

**Umbilical cord** - embryonic/fetal structure which carries embryonic/fetal blood vessels to and from the fetal component of the placenta. This will be covered in subsequent lectures.

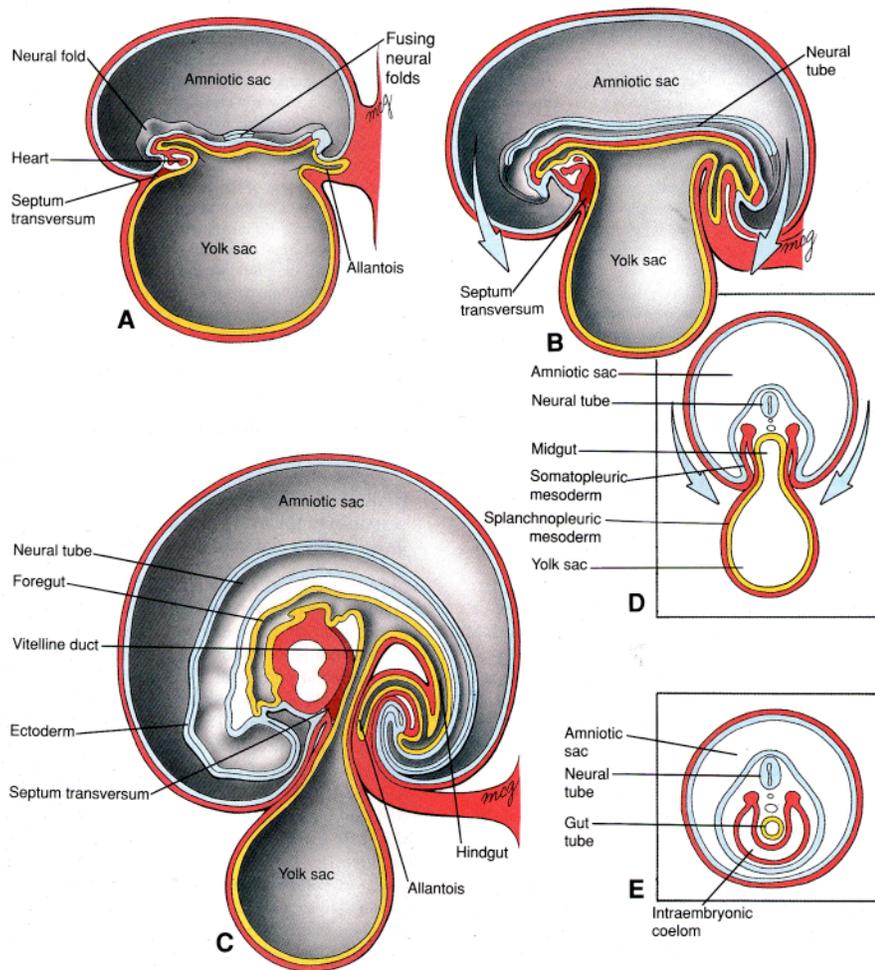
## Lecture notes:

At the end of gastrulation, the embryo is a flat trilaminar disk which is in contact with the extra-embryonic tissues at all of its surfaces (Fig. 2-1). During the 4th week there is differential growth of



**Fig. 2-1.** Sections through a 21-day embryo. The cranial and caudal portions of the paraxial mesoderm have become organized into somitomeres, and the four occipital and first two cervical somitomeres have differentiated into somites. The seven most cranial somitomeres never become somites. The dotted line indicates the level of the transverse section. At this level, the lateral plate mesoderm contains the rudiment of the intraembryonic coelom.

selected parts of the embryo. The amnion and embryonic disc grow vigorously but the yolk sac does not. Because the yolk sac is attached to the ventral rim of the disc, the expanding disk balloons into a 3D, more or less cylindrical shape. The dorsal structures of notochord, brain and somites stiffen this axis such that the flexion takes place at the thin, flexible outer rim of the disc. Cephalocaudal and lateral flexion commence at approximately the same time (days 22-28) but we shall discuss them separately (see Fig. 2-2).



**Fig. 2-2.** The process of cephalocaudal and lateral folding that transforms the embryo from a flat disc to a three-dimensional vertebrate body form. As folding occurs, the embryo grows more rapidly than the yolk sac, the cavity of which remains continuous with the developing gut tube through the narrowing vitelline duct. The septum transversum forms cranial to the cardiogenic area in the germ disc, *A*, and is translocated to the future lower thoracic region through the folding of the cranial end of the embryo, *B*, *C*. The allantois and connecting stalk combine with the yolk sac and vitelline duct through the folding of the caudal end of the embryo, *A-C*. Fusion of the ectoderm, mesoderm, future coelomic cavities, and endoderm from opposite sides is prevented in the immediate vicinity of the vitelline duct, *D*, but not in the more cranial and caudal regions, *E*.

**Cephalocaudal flexion:** The cranial rim of the embryo contains the buccopharyngeal membrane (BPM, See Lecture 1) and cranial to the BPM is the cardiogenic area (gives rise to the heart) = head fold (see definitions). Due to the rapid growth of the forebrain (cephalic neural plate) the cranial rim including the BPM and cardiogenic area folds ventral (day 22), forming the ventral surface of the future face, neck and chest and bringing the heart into its thoracic position. Another consequence of this

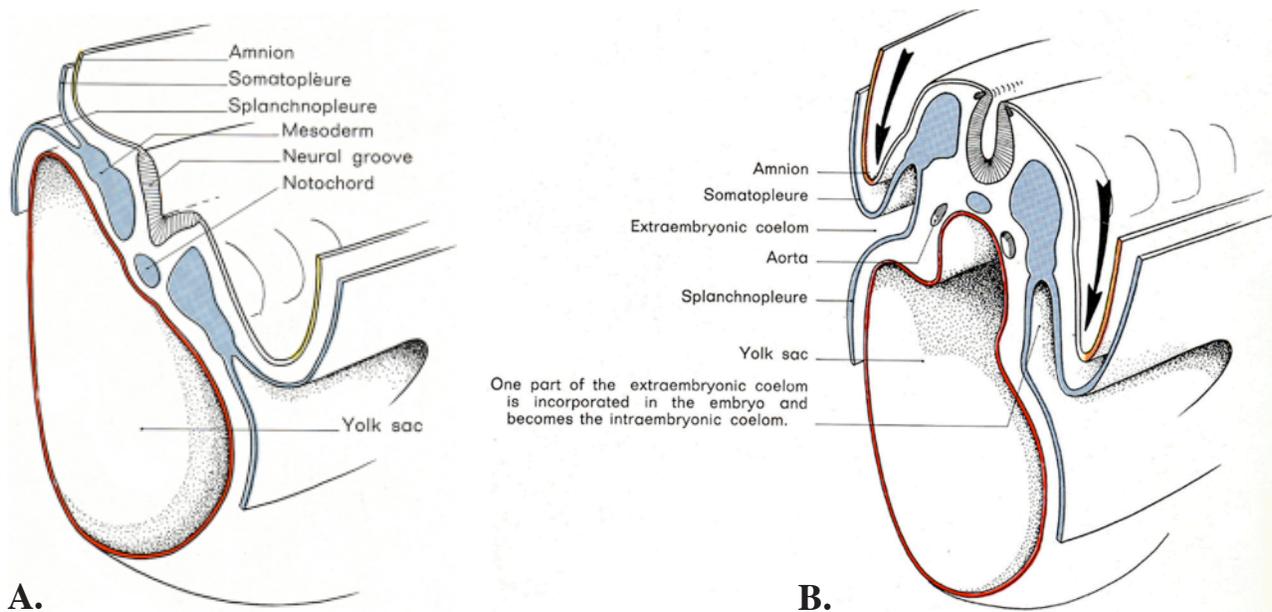
folding is the repositioning of the septum transversum from the cranial rim to the thorax, below the heart. This mesodermal structure partitions the coelom into thoracic and abdominal cavities (Fig. 2-2 A-C).

Starting on day 23 a similar process occurs at the caudal edge of the embryo. This caudal flexion brings the cloacal membrane onto the ventral surface of the embryo. It also results in the more ventral location of the connecting stalk so that it merges with the neck of the yolk sac (Fig. 2-2 A-C).

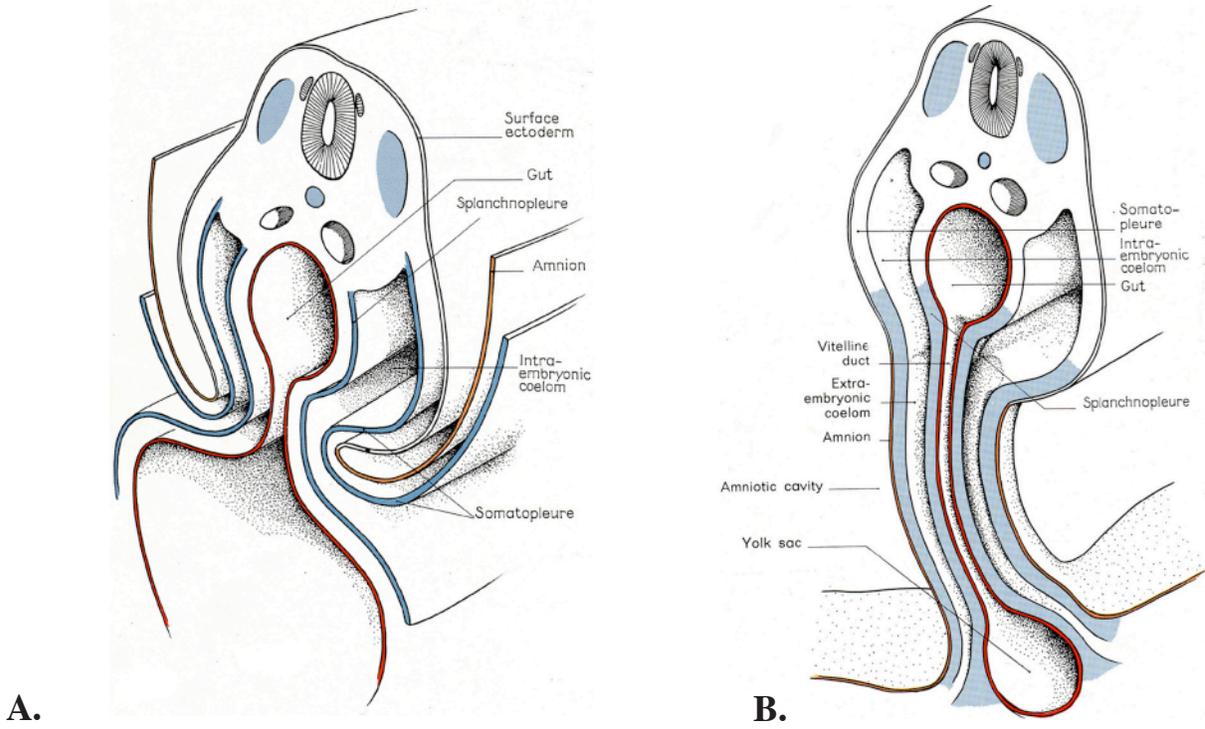
**Lateral flexion:** The lateral plate mesoderm, in the trunk region and around the developing heart, splits into somatopleure and splanchnopleure (Fig. 2-3). These flaps of mesoderm fold toward the ventral mid-line and meet and merge everywhere but at the umbilical cord (Fig. 2-4). As they fold, the space between the two is maintained and becomes the intraembryonic coelom.

The ectoderm and amniotic membrane continue to undergo rapid growth. The ectodermal sheet will also meet at midline and fuse such that the entire surface of the body is now covered with ectoderm except at the umbilicus (Fig. 2-4). The amnion now surrounds the entire embryo (Fig. 2-2 A-C). The endodermal layer also meets at midline and fuses forming the gut tube (Fig. 2-5A). Fusion of the layer is complete except at the midgut level. Here the gut tube remains open via the vitelline duct to the yolk sac (Fig. 2-4B). This opening is very important in gut development and will be discussed later.

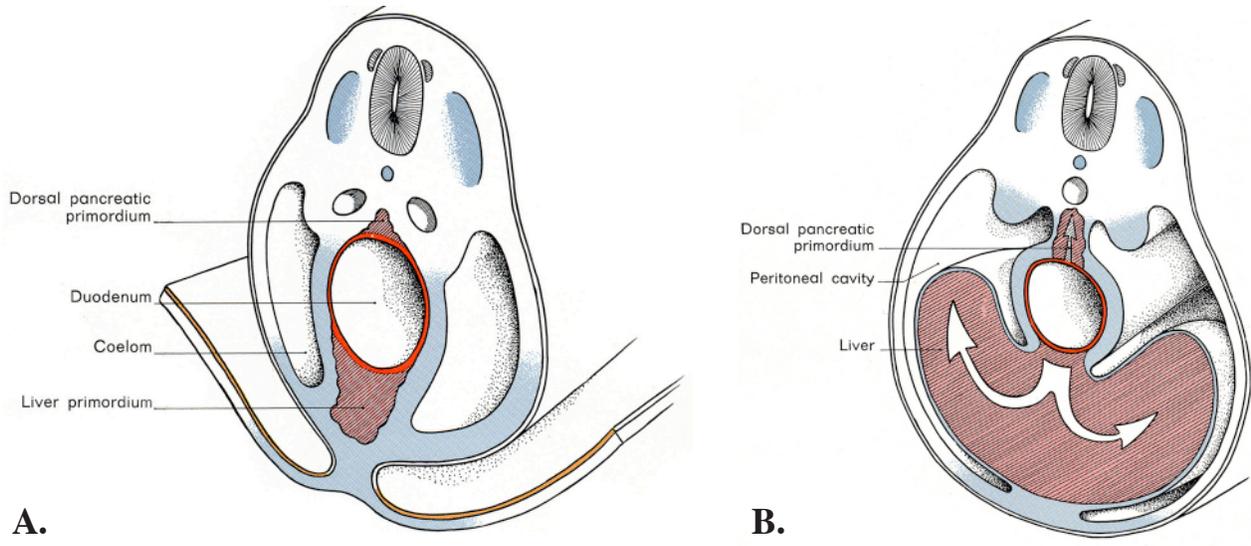
Another consequence of both cephalocaudal and lateral flexion is the narrowing/constriction of the yolk sac (Figs. 2-2, 2-4).



**Fig. 2-3.** In the umbilical region, closure remains incomplete until birth; here the structures of the umbilical cord pass into the embryo. **A.** Before the beginning of flexion, the embryo is flat, lying between the amniotic cavity and the yolk sac. **B.** The lateral edges swing ventrally (arrows). The yolk sac begins to differentiate.

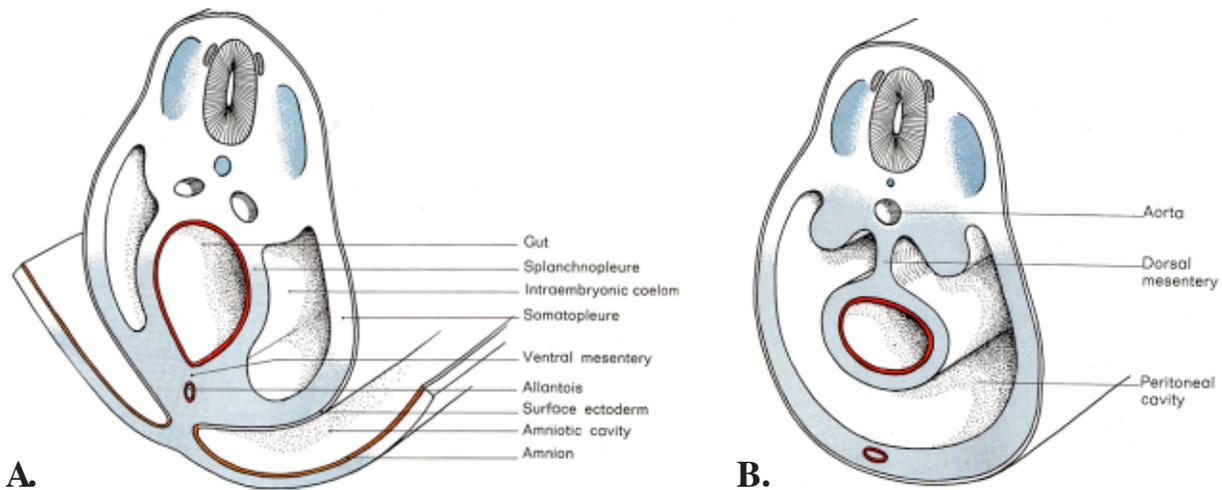


**Fig 2-4.** **A.** The ventral wall begins to form. The gut is delineated, surrounded by intraembryonic coelom. **B.** At the level of the umbilicus, the ventral wall does not close completely.

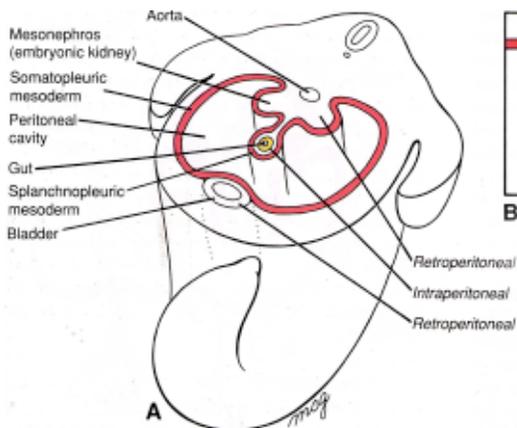


**Fig. 2-5.** **A.** The section goes through the duodenal region. At this level, the endodermal lining gives rise dorsally to one of the pancreatic primordia, and ventrally to the liver primordium. **B.** Extensive development of the liver primordium within the ventral mesentery leads, at this level, to partial filling of the coelomic cavity.

**Suspension of the gut tube:** Initially the gut tube is suspended by both a ventral and dorsal mesentery (Fig. 2-6). The former disappears and the gut tube is now attached to just a dorsal mesentery. Organs so suspended are deemed peritoneal. In some areas of the gut tube this mesentery is resorbed, as is the case for the ascending and descending colon. Such organs are deemed to be secondarily retroperitoneal (Fig. 2-7). Other organs such as the kidney and bladder develop behind the peritoneum and are retroperitoneal.



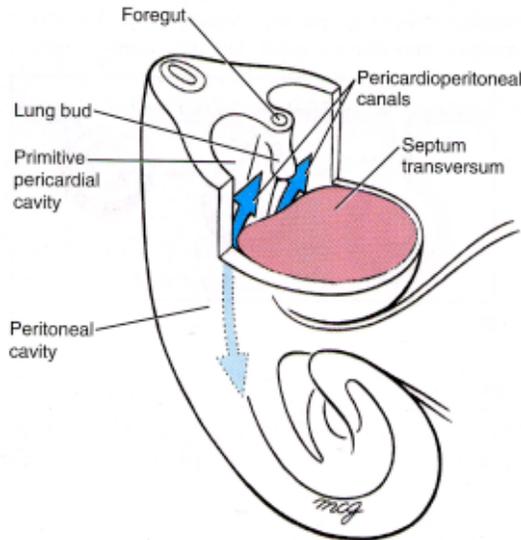
**Fig. 2-6.** **A.** The ventral wall is closed, the gut is connected to it by a temporary ventral mesentery. The dorsal mesentery has not yet differentiated. **B.** The ventral mesentery is resorbed. The intraembryonic coelom has become the peritoneal cavity. The gut is now attached to the body wall only by the definitive dorsal mesentery.



**Fig. 2-7.** The distinction between intraperitoneal, retroperitoneal, and secondarily retroperitoneal positions of the viscera. **A.** Viscera suspended within the peritoneal cavity by a mesentery are called intraperitoneal, whereas organs embedded in the body wall and covered by peritoneum are called retroperitoneal. **B.** The mesentery suspending some intraperitoneal organs disappears as both mesentery and organ fuse with the body wall. These organs are then called secondarily retroperitoneal.

**Formation of the peritoneal, pleural and pericardial cavities:**

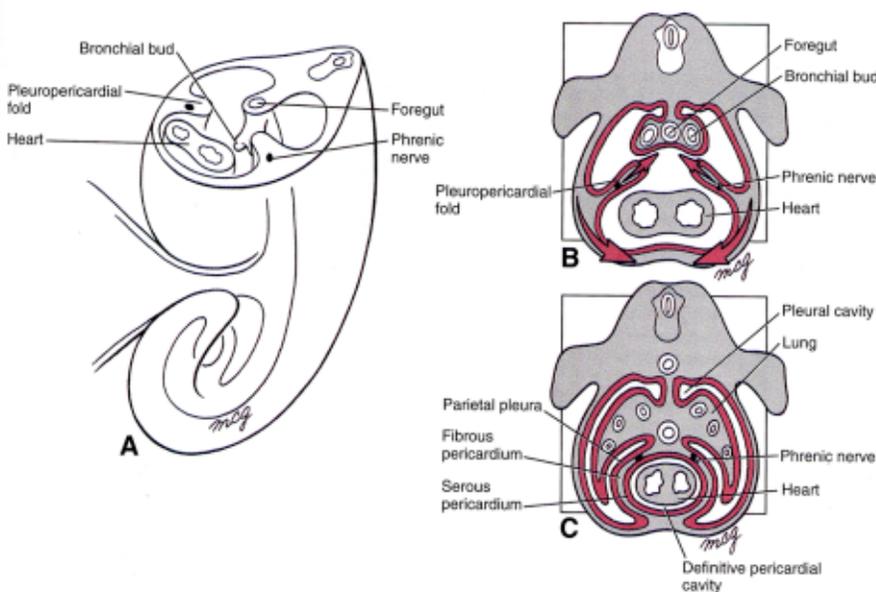
Separation of the abdominal and thoracic cavities. As mentioned above, the consequences of lateral folding results in the incorporation of an extra-embryonic compartment into the embryo = the coelom. The first partitioning of this coelom into thoracic and abdominal spaces is due to the repositioning of the septum transversum (Figs. 2-2, 2-8). Myoblasts (muscle precursors from the paraxial mesoderm) will enter the septum transversum and differentiate there into striated muscle.



**Fig. 2-8.** In the future thoracic region, the septum transversum forms a ventral partition partially separating the intraembryonic coelomic cavity into a primitive pericardial cavity superiorly and a peritoneal cavity inferiorly. These cavities remain in continuity through the posterior pericardioperitoneal canals (arrows).

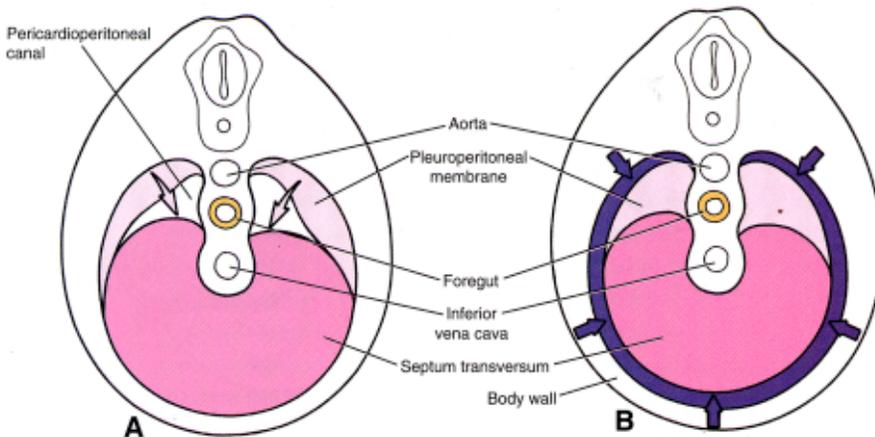
However, the primitive pericardial (thoracic) cavity is in continuity with the peritoneal via the pericardioperitoneal canals.

The segregation of the pleural from the pericardial cavity. The definitive pleural and pericardial cavities are separated by the growth of the pleuropericardial folds. These are flaps of body wall which extend in the coronal plane, meet at the midline and fuse with the foregut mesenchyme (Fig. 2-9). These flaps divide the space into a pericardial and two pleural cavities. The pleural cavities communicate with the peritoneal via the pericardialperitoneal canals (yes I know that this looks like a misnomer but there you go!) that run dorsal to the septum transversum (Fig. 2-9).



**Fig.2-9.** Subdivision of the primitive pericardial cavity. A, During the fifth week, coronal pleuropericardial folds grow out from the lateral body wall toward the midline, where they fuse with each other and with mesoderm associated with the esophagus. Simultaneously, the roots of these folds migrate ventrally so that they ultimately originate from the ventral body wall. B, The phrenic nerves initially embedded in the body wall are swept into these developing partitions. C, The pleuropericardial folds with their associated serous membrane form the pericardial sac and transform the primitive pericardial cavity into a definitive pericardial cavity and right and left pleural cavities.

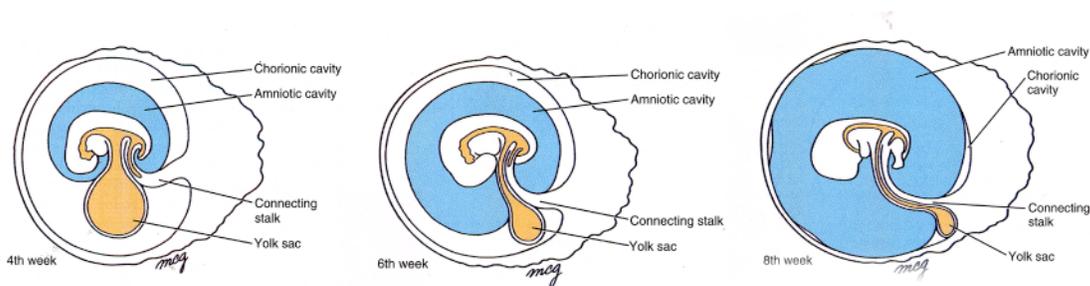
**Closing the pericardioperitoneal canals:** The closing of the pericardioperitoneal canals (which are now openings between the pleural and pericardial cavities) is accomplished by the growth of the pleuroperitoneal membranes. These are again flaps of body wall that grow medially in an oblique line connecting the root of the 12th rib with the tips of ribs 7-12. The membrane fuses with the posterior margin of the septum transversum, sealing the canals (Fig. 2-10). The left canal is larger than the right and takes longer to close hence most congenital diaphragmatic hernias occur on this side.



**Fig. 2-10.** A, B, Closure of the pericardioperitoneal canals. Between weeks 5 and 7, a pair of horizontal pleuroperitoneal membranes grow from the posterior body wall to meet the posterior edge of the septum transversum, thus closing the pericardioperitoneal canals. These membranes form the posterior portions of the diaphragm and completely seal off the pleural cavities from the peritoneal cavity.

**The diaphragm.** This musculotendinous structure is formed from: the septum transversum, the pleuroperitoneal membranes, paraxial (somite) mesoderm and the esophageal mesenchyme. As the myoblasts enter the septum transversum they are thought to bring their innervation (the phrenic nerve) with them. The outer rim of the diaphragm is innervated by the spinal nerves T7-T12.

**The maturation of the umbilical cord:** As mentioned above, the tail fold brings the connecting stalk and yolk sac together. The amnion takes origin from the umbilical root. The continued expansion of the amnion creates a tube of amniotic membrane enclosing the connecting stalk and yolk sac which now = the umbilical cord (Figs 2-4, 2-11). As the cord elongates, the vitelline duct continues to narrow and the yolk sac remains in the umbilical sheath. Yolk sac and vitelline duct will disappear before birth. The umbilical arteries and veins will develop in the connecting stalk. The will be covered in more detail in a later lecture).



**Fig. 2-11.** The rapidly expanding amniotic cavity fills with fluid and obliterates the chorionic cavity between weeks 4-8.