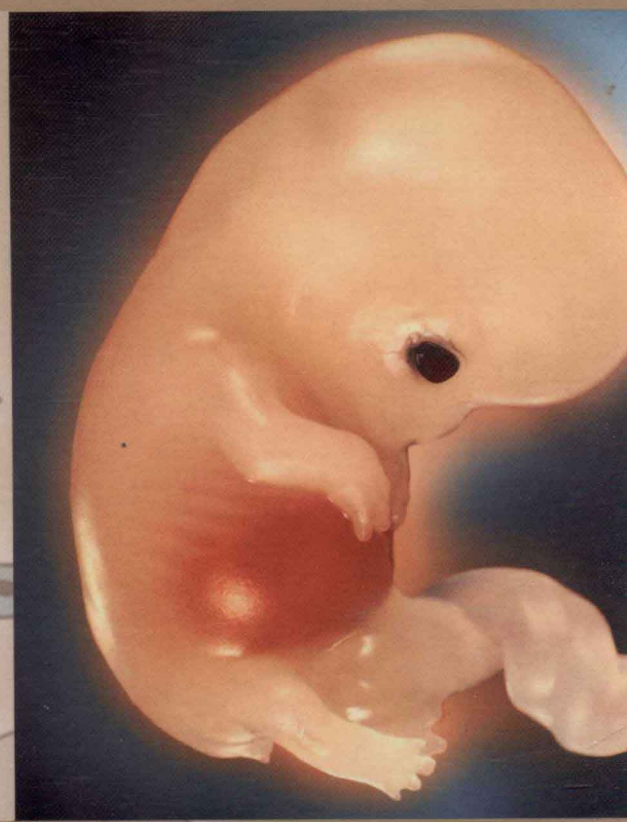
Langman's Essential Medical Embryology

T. W. Sadler



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Langman's Essential Medical Embryology

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To all students trying to learn embryology.

PREFACE

This first edition of *Langman's Essential Medical Embryology* represents the first truly "essentials" version of the topic that provides a concise but thorough description of embryology and its clinical significance. It is a unique combination of text and figures that, together, convey important concepts and an understanding of the subject. Also, included is *Simbryo,* an interactive CD-ROM that demonstrates normal embryological events and the origins of some birth defects. This unique program offers six original vector art animation modules that illustrate the complex, three-dimensional aspects of embryology. Together, *Langman's Essential Medical Embryology* and *Simbryo* provide the most comprehensive and understandable presentation of the subject in the most concise format available.

Langman's Essential Medical Embryology is a combination of concise text and figures that must be used together to gain comprehension of the subject. Figures have been grouped to better illustrate key points, which are explained succinctly. The artwork is extensive and includes 4-color line drawings and scanning electron micrographs. Each chapter also contains clinical material, including figures, to illustrate how important embryology is to understanding the origin, treatment, and prevention of birth defects. Also provided is an overview of the key genes involved in normal development and the origin of birth defects.

Embryology is a fascinating subject with relevance for many types of health care and public health officials. Serious birth defects occur in approximately 6% of children and are the leading cause of infant mortality. Thus, understanding embryology is the first step toward their prevention and treatment. Hopefully, you will find that *Langman's Essential Medical Embryology* makes the learning process simpler and easier than it has ever been.

T.W. Sadler
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CHAPTER 1

Introduction: Basic Principles of Development

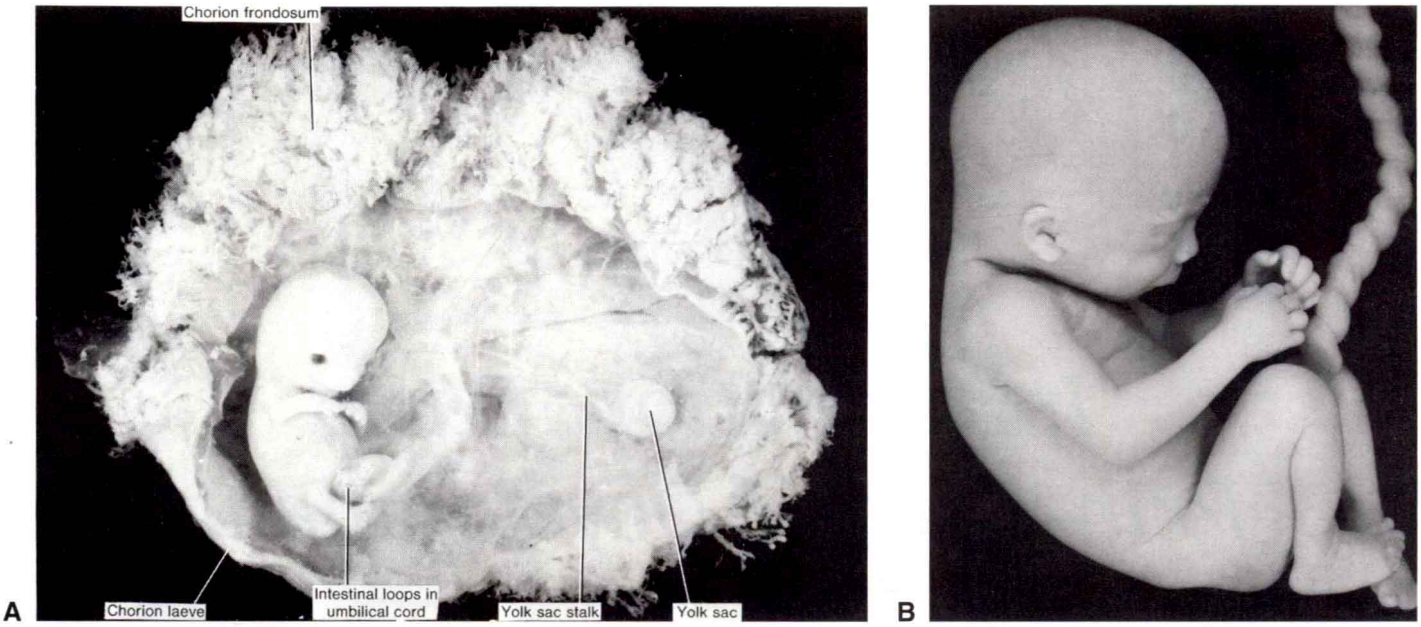


FIGURE 1.1. **Embryology** is the study of development of an organism from fertilization of the ovum—the single cell stage—through the period of **organogenesis**, when primordia of the organ systems are established. In the human, this time frame encompasses the first **8 weeks** of pregnancy (**A**). At that point, the developing human enters the **fetal period**, when differentiation continues and weight and length are increased (**B**). At the end of 8 weeks, the embryo's **crown–rump length** (CRL), the measurement from the top of the head to the rump, is approximately 3 cm, and it weighs 8 to 10 g. At birth (38 weeks), the infant's CRL is 35 cm, and it weighs 3200 g. So how does an embryo progress from a single cell to nearly a complete organism in a period of 8 weeks? The process is complex but not daunting to understand, especially now that many of the molecular signals regulating development are being elucidated. Several cellular events are essential to the process: (1) Cell proliferation increases cell number in preparation for cell differentiation. Cell division (cycle) times in the embryo are as little as 4 hours, so there can be a 32-fold increase in cell number in a 24-hour period. Such short cell cycle times begin at very early stages but also occur in each organ system as that system initiates its development. These proliferative phases are highly sensitive to insult from genetic or environmental factors. Consequently, the embryo itself, followed by each organ system, passes through a stage when it is most sensitive to these insults. If such an insult occurs very early, the embryo usually dies; if it occurs later during organogenesis, then one or more organs may develop abnormally, resulting in one or more birth defects. (2) Cell migration occurs as cells move into position to create differentiated cell types. Once again, this is a vulnerable time for cells, and they may be affected directly or indirectly via the matrix through which they travel. (3) Cell differentiation is the completion of cell development, when cells assume their ultimate phenotype. As this process is initiated, cell proliferation decreases and cells become less vulnerable to insult.

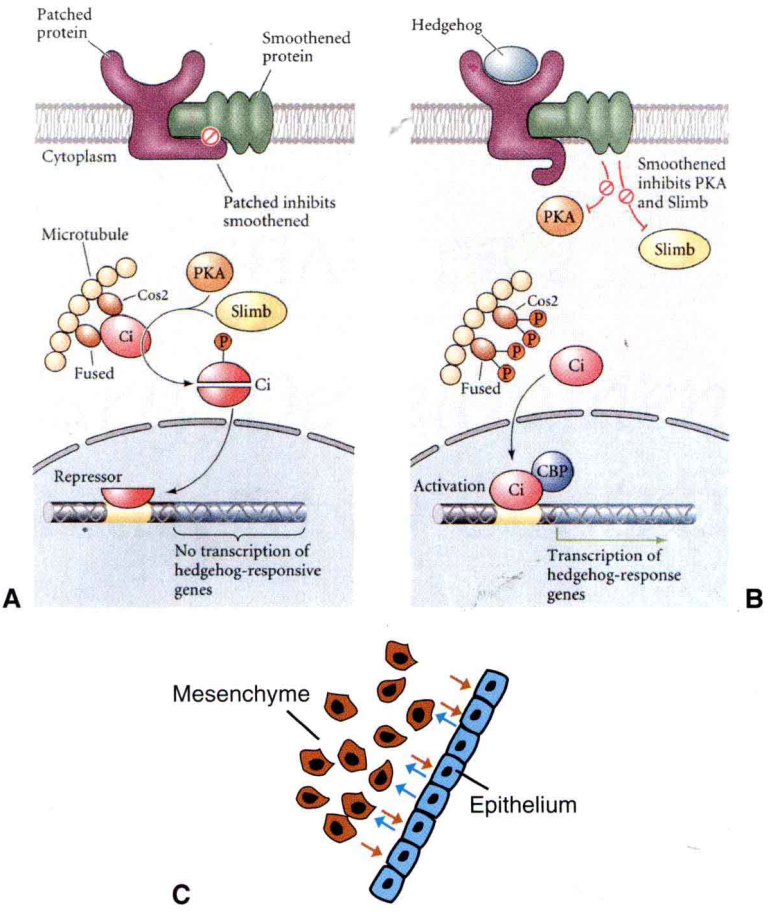


FIGURE 1.2. The molecular signals responsible for many of these cellular phenomena have been identified. For example, many genes regulating the cell cycle have been described and their roles determined. Likewise, regulatory genes for cell-to-cell communication as well as tissue interactions have been delineated. Regulation of these events invariably depends on genetic cascades involving signal molecules and their receptors, such as **growth factors** and **morphogens** together with **transcription factors** that code for DNA-binding proteins. These proteins bind to DNA and regulate expression of downstream genes. A classic example of such a signaling pathway, used repeatedly by embryos, involves the secreted morphogen *sonic hedgehog* (*SHH;* **A** and **B**). In the absence of *SHH,* its membrane receptor patched inhibits another protein called smoothened. Without smoothened activity, the cubitus interruptus (Ci) protein is bound to microtubules by Cos2 and fused proteins, where it is cleaved by protein kinase A (PKA) and slimb proteins. A cleaved portion of the Ci protein then binds to DNA and inhibits transcription of other genes (**A**). Once SHH arrives and binds to its receptor, patched, smoothened is activated, which, in turn, inactivates the Ci cleaving proteins PKA and slimb. As a result, Ci remains intact and is released from the microtubules when Cos2 and fused are inactivated by phosphorylation. Now Ci can bind to DNA and act as a transciptional activator of **SHH** response genes (**B**). Note that this pathway is activated by inhibiting an inhibitor, another recurring theme during embryogenesis. Several families of growth factors and morphogens exist, including members of the WNT, transforming growth factor-β (TGF-β; includes nodal and BMPs), fibroblast growth factor (FGF), and SHH families. These families are large, with some including 15 or more members, which increases complexity but also provides many avenues and variations for regulatory control. During organogenesis, these factors regulate many developmental events, and one of the most common of these involves **epithelial-mesenchymal interactions** (**C**). Virtually all organ systems depend on this type of interaction to initiate their differentiation. From the eye, to the limb, to the gut, to the gonads, communication between epithelial and mesenchymal tissue types is essential. Molecular signals pass from one to the other using growth factors and morphogens as both types of tissues are instructed to differentiate into their definitive structures (**C**). This interaction is fundamental to embryonic development and represents another vulnerable target for disruption. The efficiency of the process of embryogenesis is not great, and sensitivity to genetic or environmental alteration is a real issue. In fact, over 50% of fertilized ova are aborted (most so early in development that a woman never realizes she has conceived), and, of those that are aborted, over 50% have chromosomal abnormalities. Furthermore, 4% to 6% of liveborn infants suffer from a serious structural defect, e.g., cleft palate or neural tube defect. Most of the insults occur during the first 8 weeks of gestation, when basic cell processes are taking place. When all of these processes culminate in a new healthy human being, however, the phenomenon of embryogenesis is an awesome event.

CHAPTER 2

Early Development: Fertilization to Gastrulation

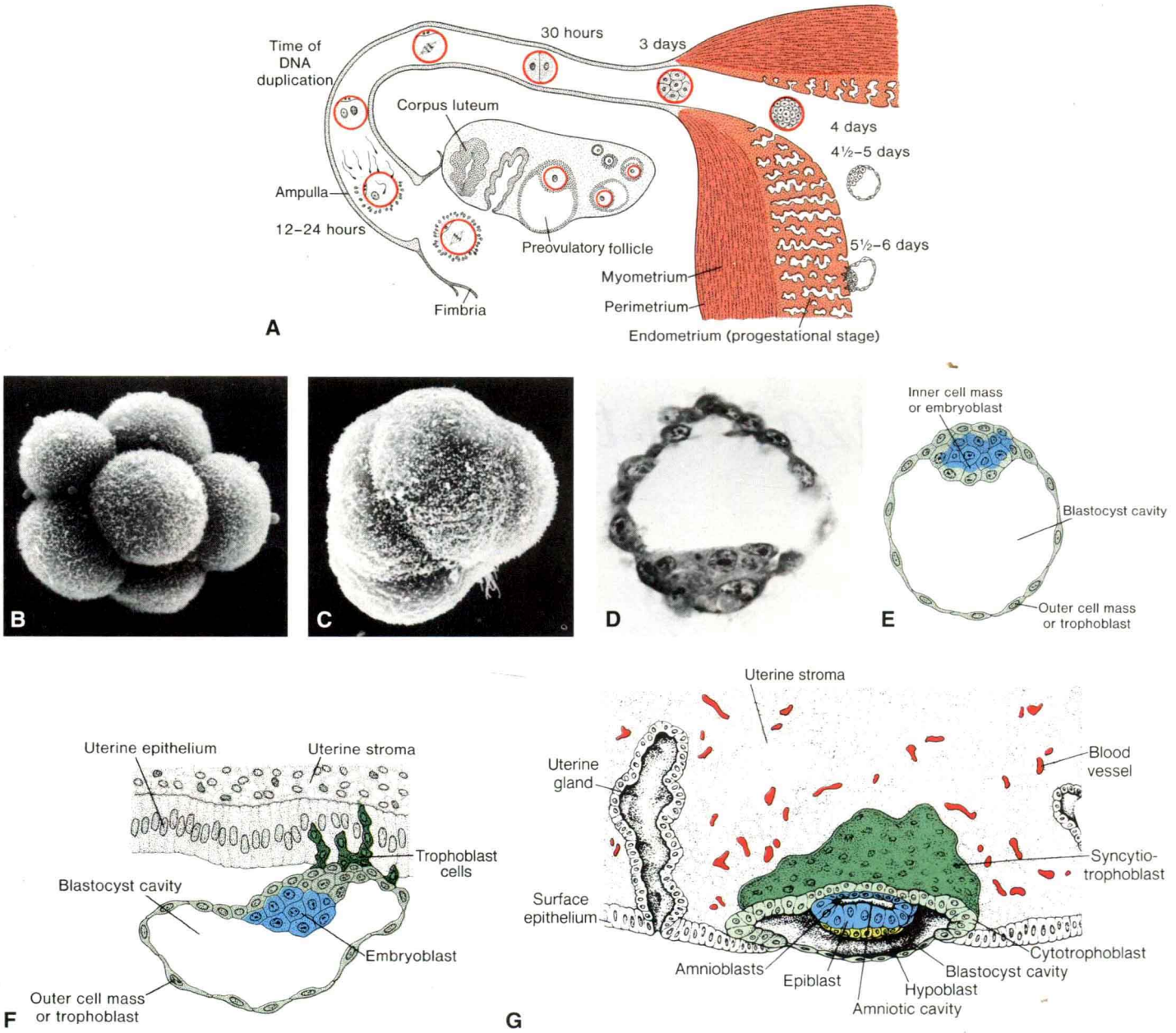


FIGURE 2.1. **Fertilization** (fusion of the sperm and egg) normally occurs in the ampullary region of the uterine (fallopian) tube within 24 hours of ovulation (**A**). Once the sperm enters the egg, the male and female pronuclei come into close contact and replicate their DNA, and cell division then occurs, creating a two-cell embryo. Cell division continues as the embryo proceeds along the uterine tube toward the uterus (**A**). Three days after fertilization, the embryo consists of a ball of cells called the **morula** (mulberry) and resides at the opening (os) of the uterine tube into the uterine cavity (**A** and **B**). At about this time, cells of the morula undergo **compaction**, a process whereby cell-to-cell contacts are maximized through tight junctions, and inner cells are segregated from outer cells (**C**). As subsequent cell divisions occur, a small group of inner cells (the **inner cell mass**, or **embryoblast**) becomes segregated from the outer cells (the **outer cell mass** or **trophoblast**). Over the next 2 days, fluid is pumped from the outside to the inside, and the morula is transformed into a hollow **blastocyst** (**D** and **E**). The inner cell mass gives rise to the entire embryo and is displaced to one pole of the blastocyst, the embryonic pole; the outer cell mass forms the outer layer of the blastocyst and contributes to development of the placenta. About the sixth day, the blastocyst implants by attaching itself to the uterine epithelium and then, over the next several days, invades this tissue (**A** and **F**). By this time, the trophoblast has differentiated into two layers: an invasive outer multinucleated cytoplasmic mass called the **syncytiotrophoblast**, and an inner proliferative layer that provides additional trophoblast cells, the **cytotrophoblast** (**F** and **G**). **Implantation** occurs when syncytiotrophoblast overlying the embryonic pole interacts with uterine epithelial cells to promote adhesion, followed by invasion of the blastocyst (**F** and **G**).

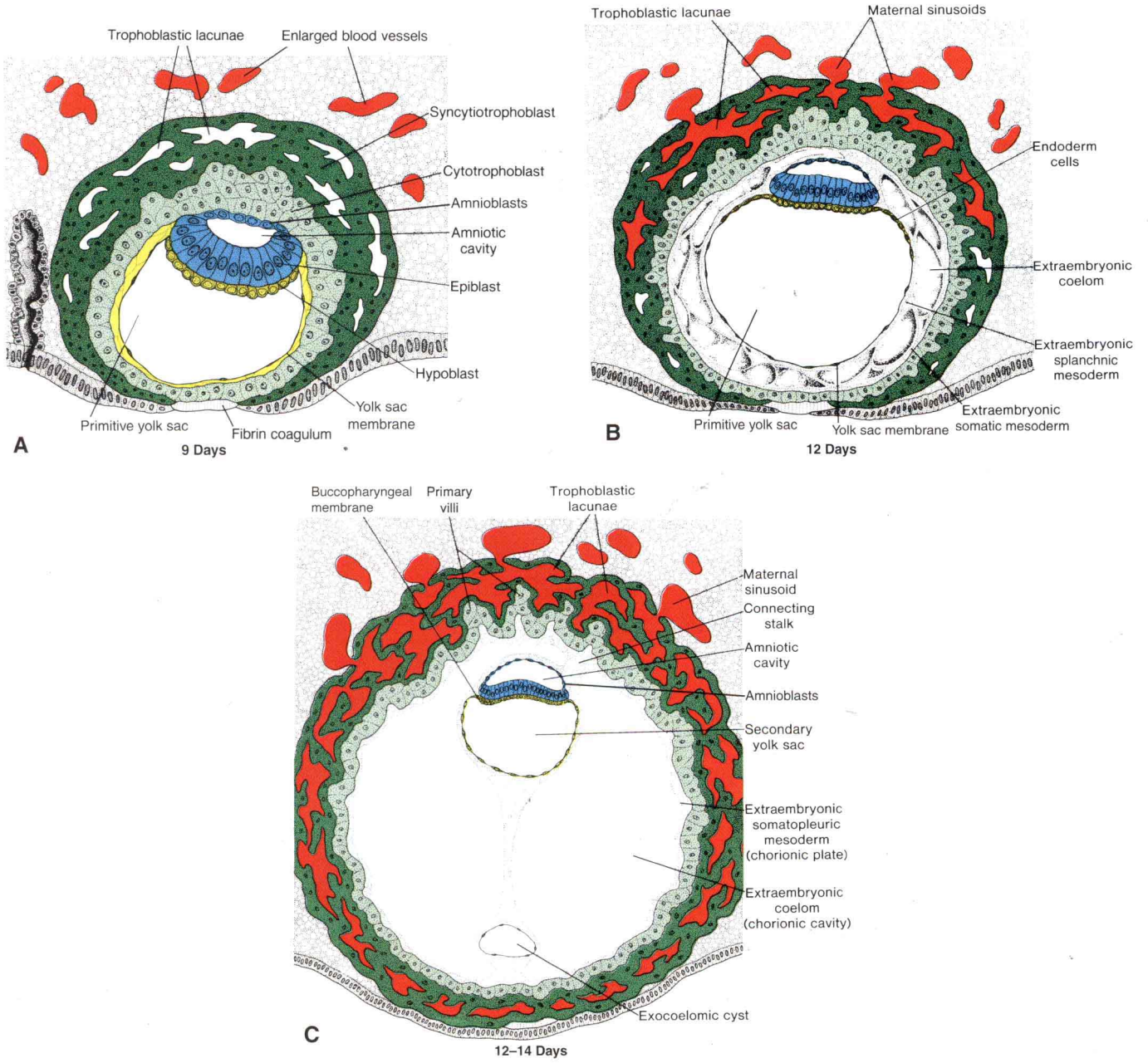
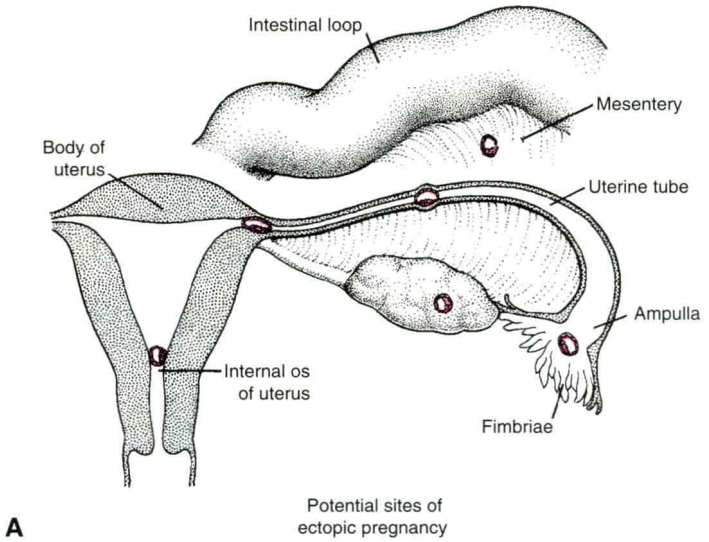
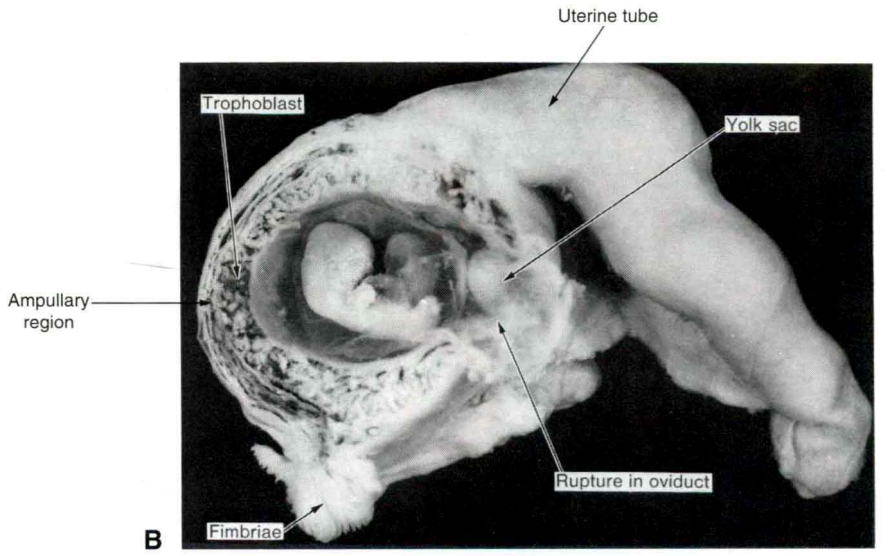


FIGURE 2.2. The second week of development is called the "week of twos." The trophoblast is differentiated into two layers, the **syncytioblast** and the **cytotrophoblast**; the **embryoblast** reorganizes into two layers, the **epiblast** dorsally and the **hypoblast** ventrally; two cavities are formed, the **amniotic cavity** dorsal to the epiblast and the **yolk sac cavity** ventral to the hypoblast; and two layers of extraembryonic mesoderm are formed between the embryo and its cavities and the cytotrophoblast (**A** and **B**). The epiblast and hypoblast appear as a slightly elongated disc (the **bilaminar germ disc**), like a cookie with no icing in the center, and it is the epiblast that will give rise to all of the tissues of the embryo. In addition, proliferation of epiblast cells at the margins of the disc forms amnioblasts that line the amniotic cavity. In a similar fashion, a primitive yolk sac is created by proliferation of hypoblast cells at the disc margins (**A**). Thus, the embryonic disc is suspended between these two cavities. Meanwhile, trophoblast cells continue to invade the uterine wall until the conceptus is surrounded by uterine tissue. By 12 to 14 days, cells of the syncytiotrophoblast erode uterine blood vessels, and maternal blood fills spaces (lacunae) that form in the syncytium, bringing nutrients closer to the developing embryo (**B** and **C**). In addition, **extraembryonic mesoderm** is formed by delamination of yolk sac cells and later by migration of cells through the primitive streak during gastrulation (**B** and **C**; Chapter 2; Fig. 2.4). Initially, this tissue forms as a single layer, but it soon separates into two layers: a layer around the yolk sac, which is the **extraembryonic splanchnic mesoderm**, and a layer over the amnion and on the inner surface of the cytotrophoblast, which is the **extraembryonic somatic mesoderm** (**C**). The two layers remain connected to each other at the **connecting stalk**, which will contribute to formation of the **umbilical cord** (**C**). The cavity between the layers is called the **extraembryonic cavity**. By the beginning of the third week, this cavity will be well defined and will form the **chorionic cavity**, while the somatic layer of extraembfyonic mesoderm will form the **chorion**. This mesoderm also will form the core of the primary villi of the placenta.





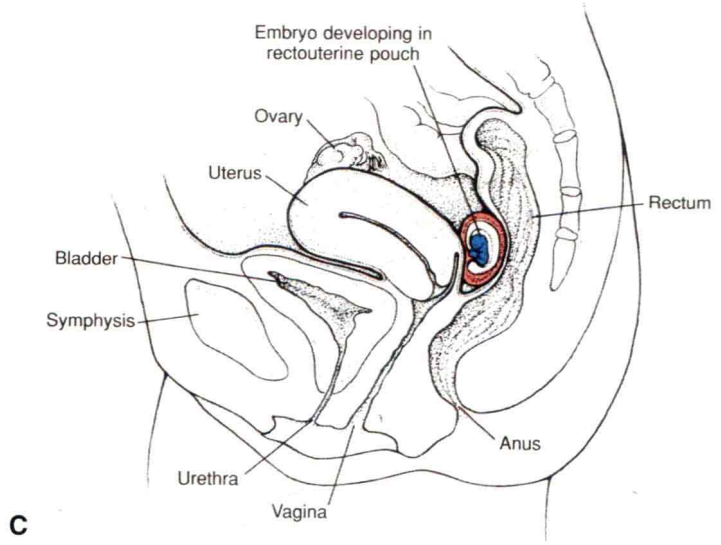


FIGURE 2.3. Because of the invasive nature of the syncytiotrophoblast, blastocysts occasionally implant at sites outside the main body of the uterus (**A**). These **ectopic pregnancies** usually occur in the ampullary region of the uterine tube (**B**), but may occur in other areas as well, even in the peritoneal cavity. In this area the most likely site is in the rectouterine (Douglas') pouch, between the uterus and rectum (**C**). All ectopic pregnancies are dangerous because of the potential for the invasive tissue of the blastocyst to cause severe bleeding.

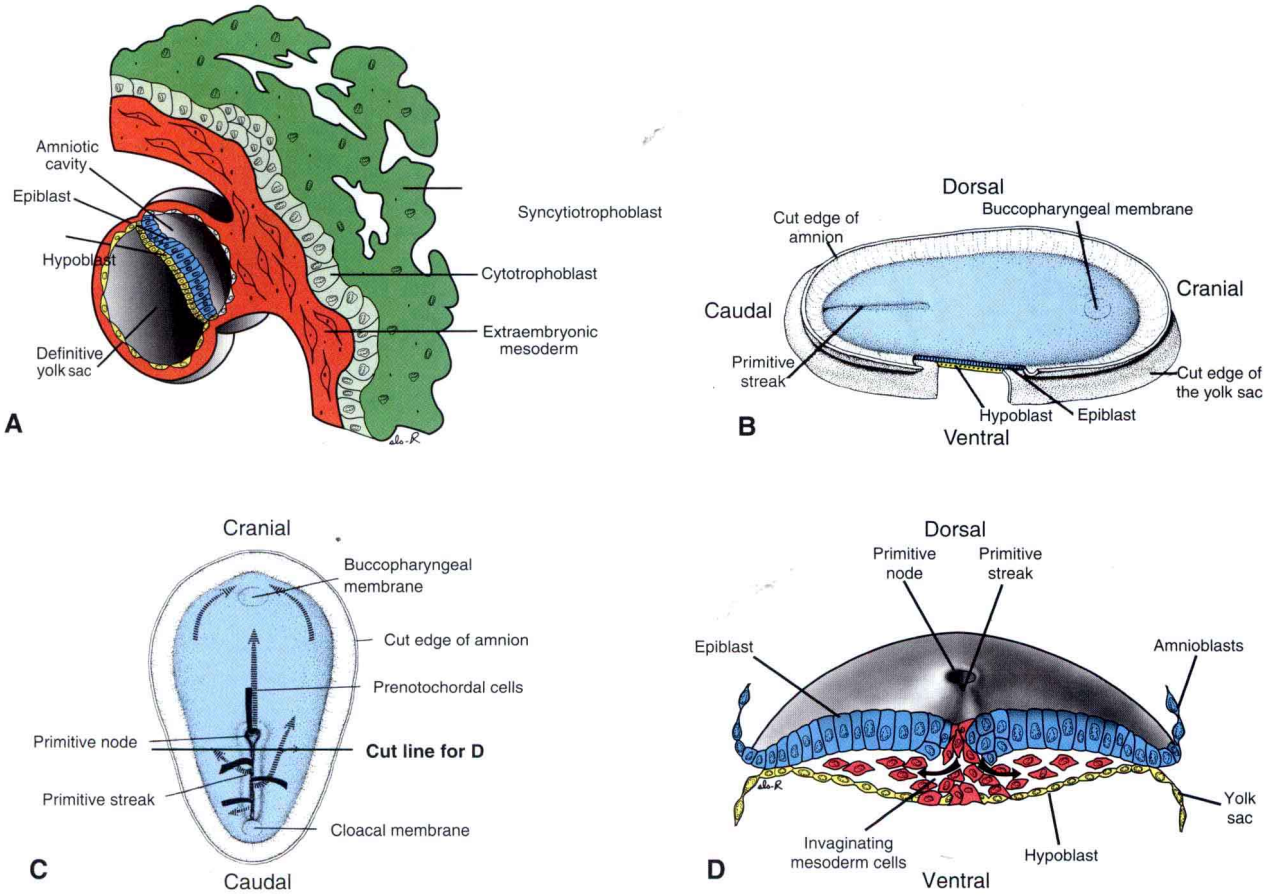


Table 2.1. **Derivatives of the Three Primary Germ Layers**

Germ Layer	Derivative
Ectoderm	Central nervous system
	Peripheral nervous system
	Epidermis, hair, nails
	Sensory epithelium: nose, ear, eye
Mesoderm	
Paraxial	Part of skull, muscles, vertebrae
Intermediate	Urogenital system
Lateral plate	
Visceral layer	Serous membranes around organs
Parietal layer	Serous membranes, body wall, limbs
Endoderm	Gut tube and its derivatives : glands, lungs, liver, gallbladder, pancreas

FIGURE 2.4. The third week is called the "week of threes." During this period, the bilaminar germ disc is transformed by the process of **gastrulation** into three germ layers: (1) **ectoderm**, which will form the central and peripheral nervous systems, the epidermis (including hair and nails), and sensory epithelia of the ear, nose, and eyes; (2) **mesoderm**, which will form muscle, bone, connective tissue, blood and blood vessels, serous membranes, and the urogenital system; and (3) **endoderm**, which will form the gut tube and all of its derivatives (glands, lungs, liver, gallbladder, and pancreas; Table 2.1. Three cavities will become defined: the **amniotic**, **yolk sac**, and **chorionic cavities** (Fig. 2.2C). At the same time, three layers will be established in the **placental villi**: the outer **syncytiotrophoblast**; the **chorionic mesoderm** on the inside; and the **cytotrophoblast** in the middle (Fig. 2.2C). **Gastrulation** is the process involving cell movements that transforms the bilaminar embryonic disc into a trilaminar structure comprised of the three primary germ layers of the embryo. It begins by formation of the **primitive streak** in the **epiblast** at the caudal end of the embryonic disc (**A** and **B**). This streak actually is a groove with a pit at its cranial end. Cells around the pit are elevated, and together the cells and pit form the **primitive node** (**C** and **D**). Once the streak and node are formed, epiblast cells migrate toward these structures and then turn into the streak and node, where they detach and continue their migration beneath the remaining epiblast (**C** and **D**). Some of these cells migrate ventrally and displace existing hypoblast cells to create a new layer, the endoderm (**D**). Others migrate between this new layer and the epiblast to form a middle layer, the mesoderm—the "icing" in the cookie (**D**). Thus, three embryonic germ layers are established: those cells remaining in the epiblast form ectoderm; those that migrate and displace the hypoblast form endoderm; and those that migrate to the middle layer form mesoderm. Note that all three layers are derived from the original epiblast.

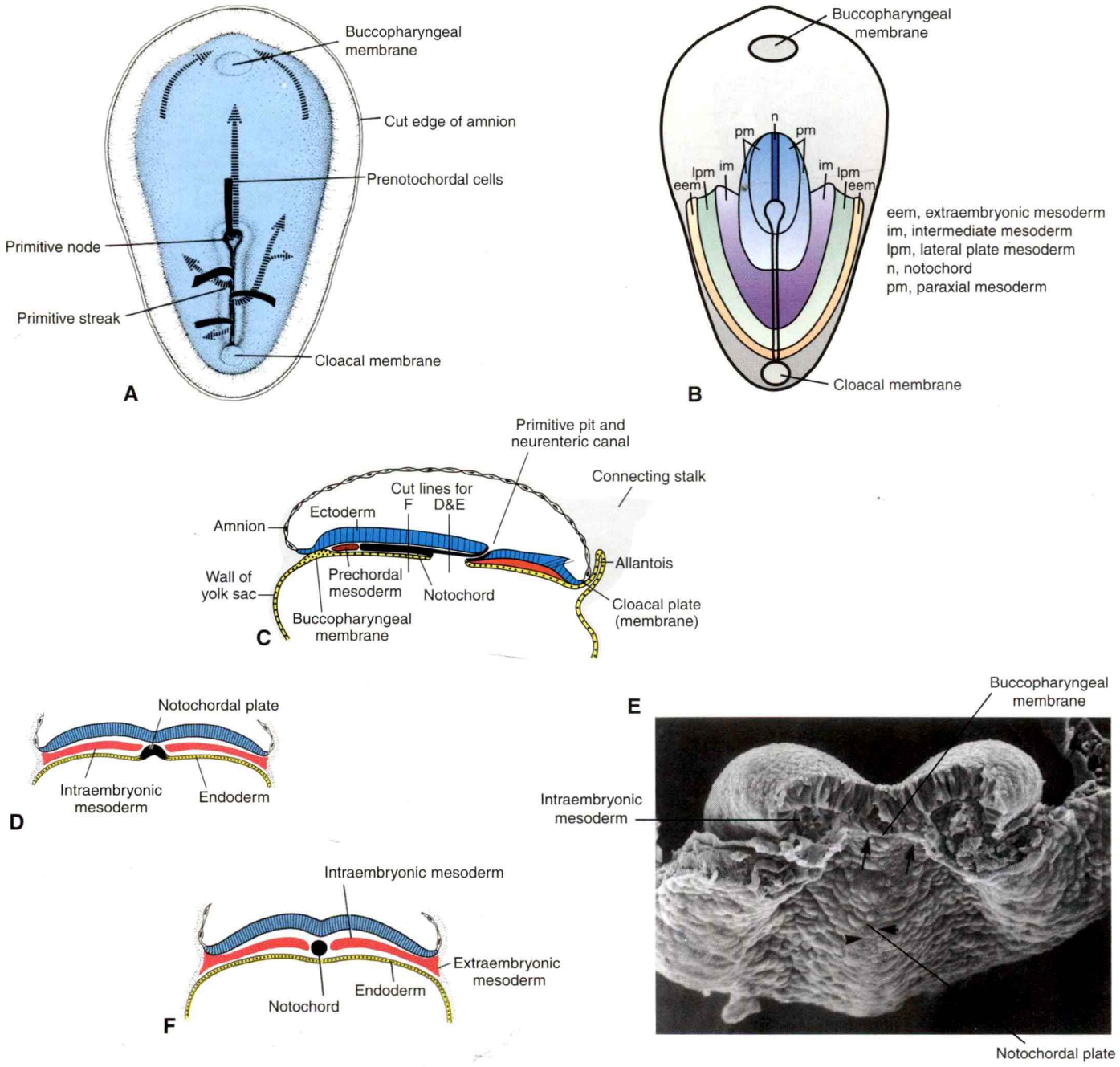


FIGURE 2.5. Epiblast cells migrate through the streak and node in specific patterns, such that their fate is determined by the region of the streak through which they pass (**A** and **B**). Thus, a "**fate map**" can be constructed showing that cells migrating through the most caudal aspect of the streak contribute to **extraembryonic mesoderm**, whereas those passing through in more cranial segments form **lateral plate**, **intermediate mesoderm**, and **paraxial mesoderm** (**B**). Some cells migrate through the most cranial aspect of the node; these form the **prechordal plate mesoderm** and **notochord** (**A** and **B**). Cells destined to form prechordal plate mesoderm migrate before notochordal cells and assume a position between the buccopharyngeal membrane and the cranial end of the notochord (**C**). Later, these cells are important for inducing forebrain development (Chapter 9; Fig. 9.10H). Notochordal cells follow those destined to form prechordal mesoderm and, at first, intercalate themselves in the endoderm layer to form the notochordal plate (**D** and **E**). Later, they detach to form the definitive notochord, a tight column of cells in close approximation to the floor of the neural tube, extending from the prechordal plate cranially to the tail bud caudally (**F**). The notochord establishes the midline and sends molecular signals essential for induction of the neural tube, somites, and other surrounding structures (Chapter 9; Fig. 9.10A–F). Only two parts of the original bilaminar disc do not become trilaminar—the **buccopharyngeal membrane** (plate) cranially and the **cloacal membrane** (plate) caudally (**B**). In these regions, epiblast and hypoblast remain tightly adherent to each other. Later, these membranes break down to form openings into the oral cavity and anus, respectively.

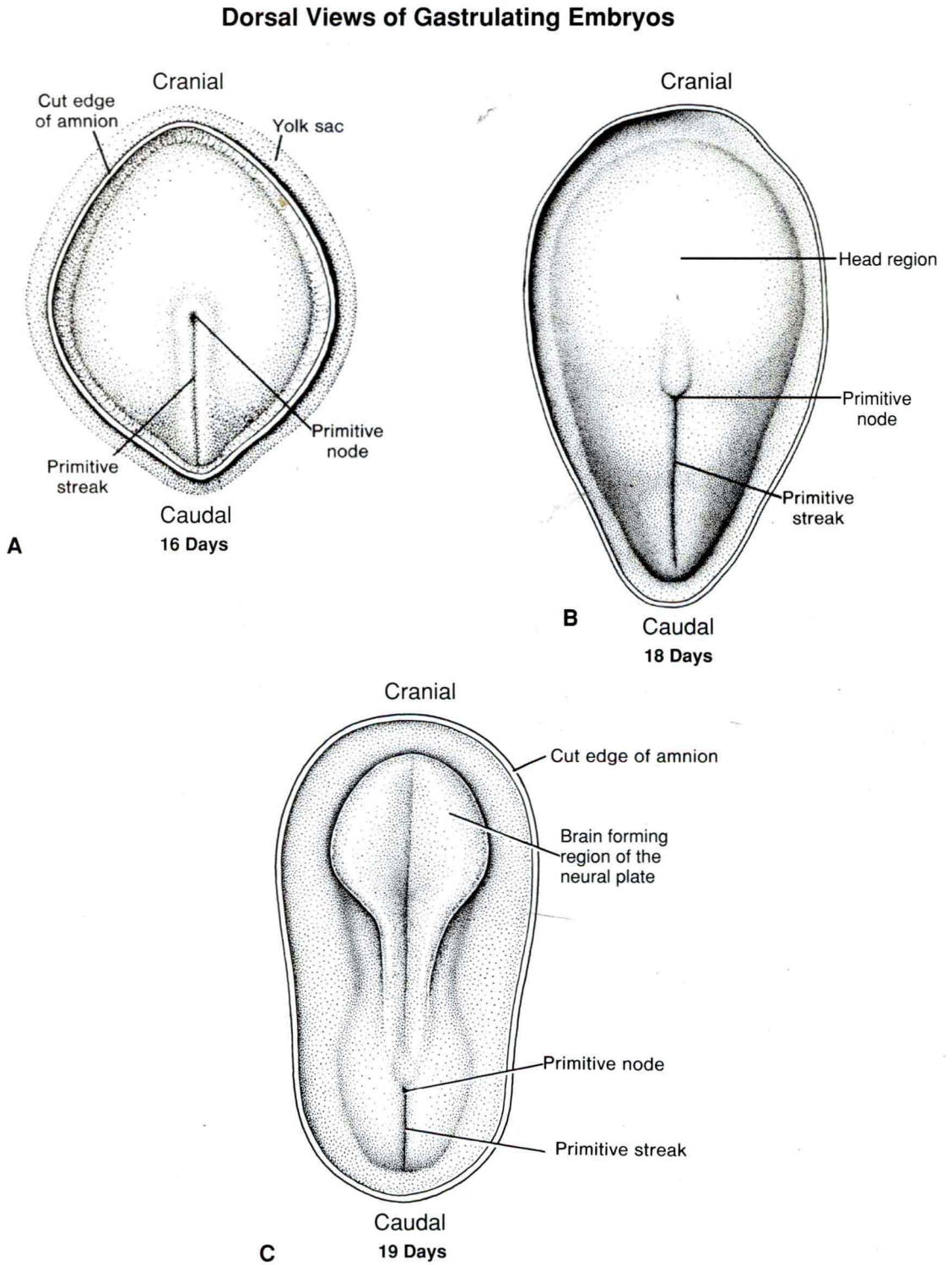


FIGURE 2.6. The process of gastrulation continues for almost 2 weeks, beginning on day 16 (**A**) and ending just before closure of the caudal-most part of the neural tube on day 28. It proceeds in a cranial to caudal sequence, with head mesoderm forming first (**B** and **C**). In fact, induction of the brain and cranial portion of the spinal cord is initiated at the same time that gastrulation continues in more caudal segments (**C**). Thus, the formation of embryonic structures typically is more advanced in cranial regions than in caudal regions of the embryo.