Third Week of Development
(Trilaminar Germ Disc)

Gastrulation: Formation of Embryonic Mesoderm and Endoderm

The most characteristic event occurring during the third week of gestation is gastrulation, the process that establishes all three germ layers (ectoderm, mesoderm, and endoderm) in the embryo. Gastrulation begins with formation of the primitive streak on the surface of the epiblast. Initially, the streak is vaguely defined, but in a 15- to 16 day embryo, it is clearly visible as a narrow groove with slightly bulging regions on either side. The cephalic end of the streak, the primitive node, consists of a slightly elevated area surrounding the small primitive pit. Cells of the epiblast migrate toward the primitive streak. Upon arrival in the region of the streak, they become flask-shaped, detach from the epiblast, and slip beneath it. This inward movement is known as invagination. Once the cells have invaginated, some displace the hypoblast, creating the embryonic endoderm, and others come to lie between the epiblast and newly created endoderm to form mesoderm. Cells remaining in the epiblast then form ectoderm. Thus, the epiblast, through the process of gastrulation, is the source of all of the germ layers, and cells in these layers will give rise to all of the tissues and organs in the embryo. As more and more cells move between the epiblast and hypoblast layers, they begin to spread laterally and cephalad. Gradually, they migrate beyond the margin of the disc and establish contact with the extraembryonic mesoderm covering the yolk sac and amnion. In the cephalic direction, they pass on each side of the prechordal plate. The prechordal plate itself forms between the tip of the notochord and the buccopharyngeal membrane and is derived from some of the first cells that migrate through the node in a cephalic direction. Later, the prechordal plate will be important for induction of the forebrain. The buccopharyngeal membrane at the cranial end of the disc consists of a small region of tightly adherent ectoderm and endoderm cells that represents the future opening of the oral cavity.

Formation of the Notochord

Prenotochordal cells invaginating in the primitive pit move forward cephalad until they reach the prechordal plate. These prenotochordal cells become intercalated in the hypoblast so that, for a short time, the midline of the embryo consists of two cell layers that form the notochordal plate. As the hypoblast is replaced by endoderm cells moving in at the streak, cells of the notochordal plate proliferate and detach from the endoderm. They then form a solid cord of cells, the definitive notochord, which underlies the neural tube and serves as the basis for the axial skeleton. Because elongation of the notochord is a dynamic process, the cranial end forms first, and caudal regions are added as the primitive streak assumes a more caudal position. The notochord and prenotochordal cells extend cranially to the prechordal plate (an area just caudal to the buccopharyngeal membrane) and caudally to the primitive pit. At the point where the pit forms an indentation in the epiblast, the neurenteric canal temporarily connects the amniotic and yolk sac cavities. The cloacal membrane is formed at the caudal end of the embryonic disc. This membrane, which is similar in structure to the buccopharyngeal membrane, consists of tightly adherent ectoderm and endoderm cells with no intervening mesoderm. When the cloacal membrane appears, the posterior wall of the yolk sac forms a small diverticulum that extends into the connecting stalk. This diverticulum, the allantoenteric diverticulum, or allantois, appears around the 16th day of development. Although in some lower vertebrates the allantois serves as a reservoir for excretion products of the renal system, in humans it remains rudimentary but may be involved in abnormalities of bladder development.

Fate Map Established During Gastrulation

Regions of the epiblast that migrate and ingress through the primitive streak have been mapped and their ultimate fates determined. For example, cells that ingress through the cranial region of the node become notochord; those migrating at the lateral edges of the

node and from the cranial end of the streak become paraxial mesoderm; cells migrating through the midstreak region become intermediate mesoderm; those migrating through the more caudal part of the streak form lateral plate mesoderm; and cells migrating through the caudal-most part of the streak contribute to extraembryonic mesoderm (the other source of this tissue is the primitive yolk sac).

Growth of the Embryonic Disc

The embryonic disc, initially flat and almost round, gradually becomes elongated, with a broad cephalic and a narrow caudal end. Expansion of the embryonic disc occurs mainly in the cephalic region; the region of the primitive streak remains more or less the same size. Growth and elongation of the cephalic part of the disc are caused by a continuous migration of cells from the primitive streak region in a cephalic direction. Invagination of surface cells in the primitive streak and their subsequent migration forward and laterally continues until the end of the fourth week. At that stage, the primitive streak shows regressive changes, rapidly shrinks, and soon disappears. That the primitive streak at the caudal end of the disc continues to supply new cells until the end of the fourth week has an important bearing on development of the embryo. In the cephalic part, germ layers begin their specific differentiation by the middle of the third week, whereas in the caudal part, differentiation begins by the end of the fourth week. Thus gastrulation, or formation of the germ layers, continues in caudal segments while cranial structures are differentiating, causing the embryo to develop cephalocaudally.

Further Development of the Trophoblast

By the beginning of the third week, the trophoblast is characterized by primary villi that consist of a cytotrophoblastic core covered by a syncytial layer. During further development, mesodermal cells penetrate the core of primary villi and grow toward the decidua. The newly formed structure is known as a secondary villus. By the end of the third

week, mesodermal cells in the core of the villus begin to differentiate into blood cells and small blood vessels, forming the villous capillary system. The villus is now known as a tertiary villus or definitive placental villus. Capillaries in tertiary villi make contact with capillaries developing in mesoderm of the chorionic plate and in the connecting stalk. These vessels, in turn, establish contact with the intraembryonic circulatory system, connecting the placenta and the embryo. Hence, when the heart begins to beat in the fourth week of development, the villous system is ready to supply the embryo proper with essential nutrients and oxygen. Meanwhile, cytotrophoblastic cells in the villi penetrate progressively into the overlying syncytium until they reach the maternal endometrium. Here they establish contact with similar extensions of neighboring villous stems, forming a thin outer cytotrophoblast shell. This shell gradually surrounds the trophoblast entirely and attaches the chorionic sac firmly to the maternal endometrial tissue. Villi that extend from the chorionic plate to the decidua basalis (decidual plate: the part of the endometrium where the placenta will form) are called stem or anchoring villi. Those that branch from the sides of stem villi are free (terminal) villi, through which exchange of nutrients and other factors will occur. The chorionic cavity, meanwhile, becomes larger, and by the 19th or 20th day, the embryo is attached to its trophoblastic shell by a narrow connecting stalk. The connecting stalk later develops into the umbilical cord, which forms the connection between placenta and embryo.

A

B

A Primary villus   B Secondary villus   C Tertiary villus