Second Week of Development
Bilaminar Germ Disc

Day-by-day account of the major events of the second week of development. However, embryos of the same fertilization age do not necessarily develop at the same rate. Indeed, considerable differences in rate of growth have been found even at these early stages of development.

Day 8

At the eighth day of development, the blastocyst is partially embedded in the endometrial stroma. In the area over the embryoblast, the trophoblast has differentiated into two layers:

(*a*) an inner layer of mononucleated cells, the **cytotrophoblast,**

(*b*) an outer multinucleated zone without distinct cell boundaries, the **syncytiotrophoblast**.

Mitotic figures are found in the cytotrophoblast but not in the syncytiotrophoblast. Thus, cells in the cytotrophoblast divide and migrate into the syncytiotrophoblast, where they fuse and lose their individual cell membranes. Cells of the inner cell mass or embryoblast also differentiate into two layers:

(*a*) a layer of small cuboidal cells adjacent to the blastocyst cavity, known as the **hypoblast layer,** and

(*b*) a layer of high columnar cells adjacent to the amniotic cavity, the **epiblast layer**. Together, the layers form a flat disc. At the same time, a small cavity appears within the epiblast. This cavity enlarges to become **amniotic cavity.** Epiblast cells adjacent to the cytotrophoblast are called **amnioblasts;** together with the rest of the epiblast, they line the amniotic cavity. The endometrial stroma adjacent to the implantation site is edematous and highly vascular. The large, tortuous glands secrete abundant
glycogen and mucus.

Day 9

The blastocyst is more deeply embedded in the endometrium, and the penetration defect in the surface epithelium is closed by a fibrin coagulum. The trophoblast shows considerable progress in development, particularly at the embryonic pole, where vacuoles appear in the syncytium. When these vacuoles fuse, they form large lacunae, and this phase of trophoblast development is thus known as the **lacunar stage**. At the abembryonic pole, meanwhile, flattened cells probably originating from the hypoblast form a thin membrane, the exocoelomic (Heuser's) membrane, that lines the inner surface of the cytotrophoblast. This membrane, together with the hypoblast, forms the lining of the **exocoelomic cavity,** or **primitive yolk sac.**

Days 11 and 12

By the 11th to 12th day of development, the blastocyst is completely embedded in the endometrial stroma, and the surface epithelium almost entirely coversthe original defect in the uterine wall. The blastocyst now produces a slight protrusion into the lumen of the uterus. The trophoblast is characterized by lacunar spaces in the syncytium that form an intercommunicating network. This network is particularly evident at the embryonic pole; at the abembryonic pole, the trophoblast still consists mainly of cytotrophoblastic cells. Concurrently, cells of the syncytiotrophoblast penetrate deeper into the stroma and erode the endothelial lining of the maternal capillaries. These capillaries, which are congested and dilated, are known as **sinusoids.** The syncytial lacunae become continuous with the sinusoids and maternal blood enters the lacunar system. As the trophoblast continues to erode more and more sinusoids, maternal blood begins to flow through the trophoblastic system, establishing the **uteroplacental circulation.** In the meantime, a new population of cells appears between the inner surface of the cytotrophoblast and the outer surface of the exocoelomic the original defect in the uterine wall. The blastocyst now produces a slight protrusion into the lumen of the uterus. The trophoblast is characterized by lacunar spaces in the syncytium that form an intercommunicating network. This network is particularly evident at the embryonic pole; at the abembryonic pole, the trophoblast still consists mainly of cytotrophoblastic cells. Concurrently, cells of the syncytiotrophoblast penetrate deeper into the stroma and erode the endothelial lining of the maternal capillaries. These capillaries, which are congested and dilated, are known as **sinusoids.** The syncytial lacunae become continuous with the sinusoids and maternal blood enters the lacunar system. As the trophoblast continues to erode more and more sinusoids, maternal blood begins to flow through the trophoblastic system, establishing the **uteroplacental circulation.** In the meantime, a new population of cells appears between the inner surface of the cytotrophoblast and the outer surface of the exocoelomic area immediately surrounding the implantation site but soon occur throughout the endometrium.

Day 13

By the 13th day of development, the surface defect in the endometrium has usually healed. Occasionally, however, bleeding occurs at the implantation site as a result of increased blood flow into the lacunar spaces. Because this bleeding occurs near the 28th day of the menstrual cycle, it may be confused with normal menstrual bleeding and, therefore, cause inaccuracy in determining the expected delivery date. The trophoblast is characterized by villous structures. Cells of the cytotrophoblast proliferate locally and penetrate into the syncytiotrophoblast, forming cellular columns surrounded by syncytium.

Cellular columns with the syncytial covering are known as **primary villi**. In the meantime, the hypoblast produces additional cells that migrate along the inside of the exocoelomic membrane. These cells proliferate and gradually form a new cavity within the exocoelomic cavity. This new cavity is known as **the secondary yolk sac** or **definitive yolk sac**. This yolk sac is much smaller than the original exocoelomic cavity, or primitive yolk sac. During its formation, large portions of the exocoelomic cavity are pinched off. These portions are represented by **exocoelomic cysts,** which are often found in the extraembryonic coelom or **chorionic cavity**. Meanwhile, the extraembryonic coelom expands and forms a large cavity, the **chorionic cavity.** The extraembryonic mesoderm lining the inside of the cytotrophoblast is then known as the **chorionic plate.** The only place where extraembryonic mesoderm traverses the chorionic cavity is in the **connecting stalk**. With development of blood vessels, the stalk becomes the **umbilical cord.**

Abnormal Implantation

The syncytiotrophoblast is responsible for hormone production, including **human chorionic gonadotropin** (hCG). By the end of the second week, quantities of this hormone are sufficient to be detected by radioimmunoassays, which serve as the basis for pregnancy testing. Because 50% of the implanting embryo's genome is derived from the father, it is a foreign body that potentially should be rejected by the maternal system. Recent evidence suggests that a combination of factors protects the conceptus, including production of immunosuppressive cytokines and proteins and the expression of an unusual major histocompatibility complex class IB molecule (HLA-G) that blocks recognition of the conceptus as foreign tissue. If the mother has autoimmune disease, for example systemic lupus erythematosus, antibodies generated by the disease may attack the conceptus and reject it. Abnormal implantation sites sometimes occur even within the uterus. Normally the human blastocyst implants along the anterior or posterior wall of the body of the uterus. Occasionally the blastocyst implants close to the internal opening os (opening) of the cervix, so that later in development, the placenta bridges the opening (**placenta previa**) and causes severe, even life-threatening bleeding in the second part of pregnancy and during delivery. Occasionally, implantation takes place outside the uterus, resulting in **extrauterine pregnancy,** or **ectopic pregnancy.** Ectopic pregnancies may occur at any place in the abdominal cavity, ovary, or uterine tube. However, 95% of ectopic pregnancies occur in the uterine tube, and most of these are in the ampulla. In the abdominal cavity, the blastocyst most frequently attaches itself to the peritoneal lining of the **rectouterine cavity,** or **Douglas' pouch**. The blastocyst may also attach itself to the peritoneal covering of the intestinal tract or to the omentum. Sometimes the blastocyst develops in the ovary proper, causing a **primary ovarian pregnancy.** In most ectopic pregnancies, the embryo dies about the second month of gestation, causing severe hemorrhaging and abdominal pain in the mother. Abnormal blastocysts are common. For

example, in a series of 26 implanted blastocysts varying in age from 7.5 to 17 days recovered frompatients of normal fertility, nine (34.6%) were abnormal. Some consisted of syncytium only; others showed varying degrees of trophoblastic hypoplasia. In two, the embryoblast was absent, and in some, the germ disc showed an abnormal orientation. It is likely that most abnormal blastocysts would not have produced any sign of pregnancy because their trophoblast was so inferior that the corpus luteum could not have persisted. These embryos probably would have been aborted with the next menstrual flow, and therefore, pregnancy would not have been detected. In some cases, however, the trophoblast develops and forms placental membranes, although little or no embryonic tissue is present. Such a condition is known as a **hydatidiformmole.** Moles secrete high levels of hCG and may produce benign or malignant (**invasive mole, choriocarcinoma**) tumors. Genetic analysis of hydatidiform moles indicates that although male and female pronuclei may be genetically equivalent, they may be different functionally. This evidence is derived from the fact that while cells of moles are diploid, their entire genome is paternal. Thus, most moles arise from fertilization of an oocyte lacking a nucleus followed by duplication of the male chromosomes to restore the diploid number. These results also suggest that paternal genes regulate most of the development of the trophoblast, since in moles, this tissue differentiates even in the absence of a female pronucleus. Other examples of functional differences in maternal and paternal genes are provided by the observation that certain genetic diseases depend on whether the defective or missing gene is inherited from the father or themother. For example, inheritance of a deletion on chromosome 15 from a father produces Prader-Willi syndrome, whereas inheritance of the same defect from the mother results in Angelman syndrome. This phenomenon, in which there is differential modification and/or expression of homologous alleles or chromosome regions, depending on the parent from whom the genetic material is derived, is known as **genomic imprinting.** Imprinting involves autosomes and sex chromosomes (in all female mammals, one X chromosome is inactivated in somatic cells and forms a **chromatin-positive body [Barr body]**) and is modulated by deoxyribonucleic acid (DNA) methylation. Certain diseases, such as Huntington’s chorea, neurofibromatosis, familial cancer disorders (Wilms’ tumors, familial retinoblastoma), and myotonic dystrophy, also involve imprinting. Fragile X syndrome, the leading cause of inherited mental retardation, may be another example of a condition based on imprinting. Preimplantation and postimplantation reproductive failure occurs often. Even in some fertile women under optimal conditions for pregnancy, 15% of oocytes are not fertilized, and 10%to 15% start cleavage but fail to implant.Of the 70% to 75% that implant, only 58% survive until the second week, and 16% of those are abnormal. Hence, when the first expected menstruation is missed, only 42% of the eggs exposed to sperm are surviving. Of this percentage, a number will be aborted during subsequent weeks and a number will be abnormal at the time of birth.