One of the most characteristic features of human embryonic development is the intimate relationship between the embryo and the mother. The fertilized egg brings little with it except genetic material. To survive and grow during intrauterine life, the embryo must maintain an essentially parasitic relationship with the body of the mother for acquiring oxygen and nutrients and eliminating wastes. It must also avoid being rejected as a foreign body by the immune system of its maternal host. These exacting requirements are met by the placenta and extraembryonic membranes that surround the embryo and serve as the interface between the embryo and the mother.

The tissues that compose the fetal-maternal interface (placenta and chorion) are derivatives of the trophoblast, which separates from the inner cell mass and surrounds the cellular precursors of the embryo proper even as the cleaving zygote travels down the uterine tube on its way to implanting into the uterine wall (see Fig. 3-17). Other extraembryonic tissues are derived from the inner cell mass. These include the amnion (an ectodermal derivative), which forms a protective fluid-filled capsule around the embryo; the yolk sac (an endodermal derivative), which in mammalian embryos no longer serves a primary nutritive function; the allantois (an endodermal derivative), which is associated with the removal of embryonic wastes; and much of the extraembryonic mesoderm, which forms the bulk of the umbilical cord, the connective tissue backing of the extraembryonic membranes, and the blood vessels that supply them.

EXTRAEMBRYONIC TISSUES

AMNION

The origin of the amniotic cavity within the ectoderm of the inner cell mass in the implanting embryo was described in Chapter 5 (see Figs. 3-17 and 5-2). As the early embryo undergoes cephalocaudal and lateral folding, the amniotic membrane surrounds the body of the embryo like a fluid-filled balloon (Fig. 7-1), allowing the embryo to be suspended in a liquid environment for the duration of pregnancy. The amniotic fluid serves as a buffer against mechanical injury to the fetus; in addition, it accommodates growth, allows normal fetal movements, and protects the fetus from adhesions.

The thin amniotic membrane consists of a single layer of extraembryonic ectodermal cells lined by a nonvascularized layer of extraembryonic mesoderm. Keeping pace with fetal growth, the amniotic cavity steadily expands until its fluid content reaches a maximum of nearly 1 L by weeks 33 to 34 of pregnancy (Fig. 7-2).

In many respects, amniotic fluid can be viewed as a dilute transudate of maternal plasma, but the origins and exchange dynamics of amniotic fluid are complex and not completely understood. There are two phases in amniotic fluid production. The first phase encompasses the first 20 weeks of pregnancy, during which the composition of amniotic fluid is quite similar to that of fetal fluids. During this period, the fetal skin is unkeratinized, and there is evidence that fluid and electrolytes are able to
FIGURE 7-1. Human embryos showing the relationships of the chorion and other extraembryonic membranes. (Modified from Carlson BM: Patten’s foundations of embryology; ed 6, New York, 1996, McGraw-Hill.)
diffuse freely through the embryonic ectoderm of the skin. In addition, the amniotic membrane itself secretes fluid, and components of maternal serum pass through the amniotic membrane.

As pregnancy advances (especially after week 20, when the fetal epidermis begins to keratinize), changes occur in the source of amniotic fluid. There is not complete agreement on the sources (and their relative contributions) of amniotic fluid in the second half of pregnancy. Nonetheless, there are increasing contributions from fetal urine, filtration from maternal blood vessels near the chorion laeve (which is closely apposed to the amniotic membrane at this stage), and possibly filtration from fetal vessels in the umbilical cord and chorionic plate.

In the third trimester of pregnancy, the amniotic fluid turns over completely every 3 hours, and at term, the fluid-exchange rate may approach 500 mL/hr. Although much of the amniotic fluid is exchanged across the amniotic membrane, fetal swallowing is an important mechanism in late pregnancy, with about 20 mL/hr of fluid being swallowed by the fetus. Swallowed amniotic fluid ultimately enters the fetal bloodstream after absorption through the gut wall. The ingested water can leave the fetal circulation through the placenta. During the fetal period, excreted urine from the fetus contributes to amniotic fluid. Clinical Correlation 7-1 discusses conditions related to the amount of amniotic fluid or substance concentrations in the fluid.

CLINICAL CORRELATION 7-1

Conditions Related to Amniotic Fluid

The normal amount of amniotic fluid at term is typically 500 to 1000 mL. An excessive amount (>2000 mL) is hydramnios. This condition is frequently associated with multiple pregnancies and esophageal atresia or anencephaly (a congenital anomaly characterized by gross defects of the head and often the inability to swallow [see Fig. 8-4]). Such circumstantial evidence supports the important role of fetal swallowing in the overall balance of amniotic fluid exchange. Too little amniotic fluid (<500 mL) is oligohydramnios. This condition is often associated with bilateral renal agenesis (absence of kidneys) and points to the role of fetal urinary excretion in amniotic fluid dynamics. Oligohydramnios also can be a consequence of preterm rupture of the amniotic membrane, which occurs in about 10% of pregnancies.

There are many components, both fetal and maternal, in amniotic fluid; more than 200 proteins of maternal and fetal origin have been detected in amniotic fluid. With the analytical tools available, much can be learned about the condition of the fetus by examining the composition of amniotic fluid. Amniocentesis involves removing a small amount of amniotic fluid by inserting a needle through the mother’s abdomen and into the amniotic cavity. Because of the small amount of amniotic fluid in early embryos, amniocentesis is usually not performed until the 13th or 14th week of pregnancy. Amniotic fluid has bacteriostatic properties, which may account for the low incidence of infections after amniocentesis is performed.

Fetal cells present in the amniotic fluid can be cultured and examined for various chromosomal and metabolic defects. More recent techniques now permit the examination of chromosomes in the cells immediately obtained instead of having to wait up to 2 to 3 weeks for cultured amniotic cells to proliferate to the point of being suitable for genetic analysis. In addition to the detection of chromosomal defects (e.g., trisomies), it is possible to determine the sex of the fetus by direct chromosomal analysis. Many cells of the amniotic fluid have been shown to possess stem cell properties. Whether or not amniotic stem cells have as broad a capacity to differentiate into as wide a variety of mature cell types as embryonic stem cells remains to be established.

A high concentration of α-fetoprotein (a protein of the central nervous system) in amniotic fluid is a strong indicator of a neural tube defect. Fetal maturity can be assessed by determining the concentration of creatinine or the lecithin/sphingomyelin ratio (which is a reflection of the maturity of the lungs). The severity of erythroblastosis fetalis (Rh disease) can also be assessed by examination of amniotic fluid.
YOLK SAC

The yolk sac, which is lined by extraembryonic endoderm, is formed ventral to the bilayered embryo when the amnion appears dorsal to the embryonic disk (see Fig. 5-2). In contrast to birds and reptiles, the yolk sac of mammals is small and devoid of yolk. Although vestigial in terms of its original function as a source of nutrition, the yolk sac remains vital to the embryo because of other functions that have become associated with it.

When it first appears, the yolk sac is in the form of a hemisphere bounded at the equatorial region by the dorsal wall of the primitive gut (see Fig. 7-1). As the embryo grows and undergoes lateral folding and curvature along the craniocaudal axis, the connection between the yolk sac and forming gut becomes attenuated in the shape of a progressively narrowing stalk attached to a more spherical yolk sac proper at its distal end. In succeeding weeks, the yolk stalk becomes very long and attenuated as it is incorporated into the body of the umbilical cord. The yolk sac itself moves nearer the chorionic plate of the placenta (Fig. 7-3).

The endoderm of the yolk sac is lined on the outside by well-vascularized extraembryonic mesoderm. Cells found in each of these layers contribute vital components to the body of the embryo. During the third week, primitordial germ cells, which arise in the extraembryonic mesoderm near the base of the allantois, become recognizable in the lining of the yolk sac (see Fig. 1-1). Soon these cells migrate into the wall of the gut and the dorsal mesentery as they make their way to the gonads, where they differentiate into oogonia or spermatogonia.

In the meantime, groups of extraembryonic mesodermal cells in the wall of the yolk sac become organized into blood islands (see Fig. 6-19), and many of the cells differentiate into primitive blood cells. Extraembryonic hematopoiesis continues in the yolk sac until about the sixth week, when blood-forming activity transfers to intraembryonic sites, especially the liver.

As the tubular gut forms, the attachment site of the yolk stalk becomes progressively less prominent, until by 6 weeks it has effectively lost contact with the gut. In a small percentage of adults, traces of the yolk duct persist as a fibrous cord or an outpouching of the small intestine known as Meckel’s diverticulum (see Fig. 15-13A). The yolk sac itself may persist throughout much of pregnancy, but it is not known to have a specific function in the fetal period. The proximal portions of the blood vessels of the yolk sac (the vitelline circulatory arc) persist as vessels that supply the midgut region.

ALLANTOIS

The allantois arises as an endodermally lined ventral outpocketing of the hindgut (see Fig. 7-1). In the human embryo, it is just a vestige of the large, saclike structure that is used by the embryos of many mammals, birds, and reptiles as a major respiratory organ and repository for urinary wastes. Similar to the yolk sac, the allantois in a human retains only a secondary function, in this case respiration. In humans, this function is served by the blood vessels that differentiate from the mesodermal wall of the allantois. These vessels form the umbilical circulatory arc, consisting of the arteries and veins that supply the placenta (see Fig. 6-26). (The postnatal fate of these vessels is discussed in Chapter 18.)

The allantois proper, which consists of little more than a cord of endodermal cells, is embedded in the umbilical cord. Later in development, the proximal part of the allantois (called the urachus) is continuous with the forming urinary bladder (see Fig. 16-2). After birth, it becomes transformed into a dense fibrous cord (median umbilical ligament), which runs from the urinary bladder to the umbilical region (see Fig. 18-19).

CHORION AND PLACENTA

Formation of the placental complex represents a cooperative effort between the extraembryonic tissues of the embryo and the endometrial tissues of the mother. (Early stages of implantation of the embryo and the decidual
reaction of the uterine lining are described in Chapter 3.) After implantation is complete, the original trophoblast surrounding the embryo has undergone differentiation into two layers: the inner cytotrophoblast and the outer syncytiotrophoblast (see Fig. 3-17D). Lacunae in the rapidly expanding trophoblast have filled with maternal blood, and the connective tissue cells of the endometrium have undergone the decidual reaction (containing increased amounts of glycogen and lipids) in response to the trophoblastic invasion.

**FORMATION OF CHORIONIC VILLI**

In the early implanting embryo, the trophoblastic tissues have no consistent gross morphological features; consequently, this is called the period of the **previllous embryo**. Late in the second week, defined cytotrophoblastic projections called **primary villi** begin to take shape (see Fig. 5-2). Shortly thereafter, a mesenchymal core appears within an expanding villus, at which point it is properly called a **secondary villus** (Fig. 7-4). Surrounding the mesenchymal core of the secondary villus is a complete layer of cytotrophoblastic cells, and outside of that is the syncytiotrophoblast. By definition, the secondary villus becomes a **tertiary villus** when blood vessels penetrate its mesenchymal core and newly formed branches. This occurs toward the end of the third week of pregnancy.

Although individual villi undergo considerable branching, most of them retain the same basic structural plan throughout pregnancy. While the placental villi are becoming established, the homeobox-containing genes, **Msx-2** and **Dlx-4** (*distalless-4*), are expressed near the interface between the trophoblast and underlying extraembryonic mesenchyme. These transcription factors are often seen at sites of epitheliomesenchymal interactions. The transcription factor **Gem-1**, which promotes an exit from the cell cycle, is expressed at branching points on the villi. Cytotrophoblastic cells on either side of the region of Gem-1 expression continue to proliferate. These form the cellular basis of new villous buds.

The terminal portion of a villus remains trophoblastic, consisting of a solid mass of cytotrophoblast called a **cytotrophoblastic cell column** (see Fig. 7-4) and a relatively thin covering of syncytiotrophoblast over that. The villus is bathed in maternal blood. A further development of the tip of the villus occurs when, under the influence of the local hypoxic environment, the cytotrophoblastic cell column expands distally, penetrating the syncytiotrophoblastic layer (Fig. 7-5). These cytotrophoblastic cells abut directly on maternal decidual cells and spread over them to form a complete cellular layer known as the **cytotrophoblastic shell**, which surrounds the embryo complex. The villi that give off the cytotrophoblastic extensions are known as **anchoring villi** (see Fig. 7-4) because they represent the real attachment points between the embryo complex and the maternal tissues.

It is important to understand the overall relationships of the various embryonic and maternal tissues at this stage of development (see Fig. 7-5). The embryo, attached by the **body stalk**, or **umbilical cord**, is effectively suspended in the **chorionic cavity**. The chorionic cavity is bounded by the **chorionic plate**, which consists of extraembryonic mesoderm overlain with trophoblast. The chorionic villi extend outward from the chorionic plate, and their trophoblastic covering is continuous with that of the chorionic plate. The villi and the outer surface of the chorionic plate are bathed in a sea of continually
exchanging maternal blood. Because of this, the human placenta is designated as the hemochorial type.*

Although chorionic villi are structurally very complex, it is convenient to liken the basic structure of a villus complex to the root system of a plant. The anchoring villus is equivalent to the central tap root; by means of the cytotrophoblastic cell columns, it attaches the villus complex to the outer cytotrophoblastic shell. The unattached branches of the floating villi (see Fig. 7-12) dangle freely in the maternal blood that fills the space between the chorionic plate and the outer cytotrophoblastic shell. All surfaces of the villi, chorionic plate, and cytotrophoblastic shell that are in contact with maternal blood are lined with a continuous layer of syncytiotrophoblast.

ESTABLISHING THE UTEROPLACENTAL CIRCULATION

One of the critical features of the developing embryonic-maternal interface is the establishment of a uteroplacental circulation that serves as the medium for bringing food and oxygen to and removing wastes from the embryo. This is accomplished by erosion of the walls of the spiral arteries of the uterus and their modification so that, as the embryo grows, they can provide an increasing flow of blood at low pressure to bathe the syncytiotrophoblastic surface of the placenta (see Fig. 7-10). Specialized invasive cytotrophoblastic cells, migrating out from the anchoring villi, invade the spiral arteries (but not the veins) and cause major modifications of their walls by secreting a specialized extracellular matrix and displacing many of the normal cellular elements of the spiral arteries. As a result, the arteries become wider, but the blood escaping from their open ends leaves at a much lower pressure than normal arterial pressure.

The first maternal fluid that bathes the embryonic trophoblast is not highly cellular, and the oxygen tension is low. During this period, the fetal erythrocytes contain embryonic hemoglobin, which is adapted to bind oxygen under low tension.

Hypoxia stimulates cytotrophoblastic cells to undergo mitosis. This may be one of the environmental conditions that underlie the rapid growth of the cytotrophoblast during the early embryonic period. After 12 weeks, when the maternal blood in the placental space contains large numbers of erythrocytes and is more highly oxygenated, the fetal erythrocytes, through an isoform switch, begin to produce fetal hemoglobin, which requires higher oxygen tension to bind oxygen efficiently. The maternal blood that leaves the spiral arteries freely percolates throughout the intervillous spaces and bathes the surfaces of the villi. The maternal blood is then picked up by the open ends of the uterine veins, which also penetrate the cytotrophoblastic shell (see Fig. 7-10).

GROSS RELATIONSHIPS OF CHORIONIC AND DECIDUAL TISSUES

Within days after implantation of the embryo, the stromal cells of the endometrium undergo a striking transforma-
tion called the decidual reaction. After the stromal cells swell as the result of the accumulation of glycogen and lipid in their cytoplasm, they are known as decidual cells (Fig. 7-6). The decidual reaction spreads throughout stromal cells in the superficial layers of the endometrium. The maternal decidua are given topographic names based on where they are located in relation to the embryo.

The decidual tissue that overlies the embryo and its chorionic vesicle is the decidua capsularis, whereas the decidua that lies between the chorionic vesicle and the uterine wall is the decidua basalis (Fig. 7-7). With continued growth of the embryo, the decidua basalis becomes incorporated into the maternal component of the definitive placenta. The remaining decidua, which consists of the decidualized endometrial tissue on the sides of the uterus not occupied by the embryo, is the decidua parietalis.

In human embryology, the chorion is defined as the layer consisting of the trophoblast plus the underlying extraembryonic mesoderm (see Fig. 7-1). The chorion forms a complete covering (chorionic vesicle) that surrounds the embryo, amnion, yolk sac, and body stalk. During the early period after implantation, primary and secondary villi project almost uniformly from the entire outer surface of the chorionic vesicle. The formation of tertiary villi is asymmetrical, however, and the invasion of the cytotrophoblastic core of the primary villi by mesenchyme and embryonic blood vessels occurs preferentially in the primary villi located nearest the decidua basalis. As these villi continue to grow and branch, the villi located on the opposite side (the abembryonic pole) of the chorionic vesicle fail to keep up and eventually atrophy as the growing embryo complex bulges into the uterine cavity (see Fig. 7-7). The region that contains the flourishing chorionic villi and that ultimately becomes the placenta is the chorion frondosum. The remainder of the chorion, which ultimately becomes smooth, is the chorion laeve (Fig. 7-8).

The overall growth of the chorionic vesicle (Fig. 7-9), with its bulging into the uterine lumen, pushes the decidua capsularis progressively farther from the endometrial blood vessels. By the end of the first trimester, the decidua capsularis itself undergoes pronounced atrophy. Within the next month, portions of the atrophic decidua capsularis begin to disappear, leaving the chorion laeve in direct contact with the decidua parietalis on the opposite side of the uterus (see Fig. 7-7). By midpregnancy, the decidua capsularis has fused with the tissues of the decidua parietalis, effectively obliterating the original uterine cavity. While the chorion laeve and decidua capsularis are undergoing progressive atrophy, the placenta takes shape in its definitive form and acts as the main site of exchange between the mother and embryo.

**FORMATION AND STRUCTURE OF THE MATURE PLACENTA**

As the distinction between the chorion frondosum and chorion laeve becomes more prominent, the limits of the
FIGURE 7-7. Relationships between the embryo and maternal decidua (pink) from the early weeks of pregnancy through the fifth month. In the 5-month-old fetus, the placenta is represented by the white tissue to the right of the fetus. (Modified from Carlson BM: Patten's foundations of embryology, ed 6, New York, 1996, McGraw-Hill.)

FIGURE 7-8. Early formation of the chorion laeve. The small bare area in this photograph of a human chorionic vesicle is a region where the chorionic villi have atrophied. This will enlarge in succeeding weeks. (From Gilbert-Barness E, ed: Potter's pathology of the fetus and infant, St Louis, 1997, Mosby.)
placenta proper can be defined. The placenta consists of a fetal and a maternal component (Fig. 7-10). The fetal component is the part of the chorionic vesicle represented by the chorion frondosum. It consists of the wall of the chorion, called the **chorionic plate**, and the chorionic villi that arise from that region. The maternal component is represented by the decidua basalis, but covering the decidua basalis is the fetally derived outer cytotrophoblastic shell. The intervillous space between the fetal and maternal components of the placenta is occupied by freely circulating maternal blood. In keeping with its principal function as an organ-mediating exchange between the fetal and maternal circulatory systems, the overall structure of the placenta is organized to provide a very large surface area (>10 m²) for that exchange.

**Structure of the Mature Placenta**

The mature placenta is disklike in shape, 3 cm thick, and about 20 cm in diameter (Table 7-1). A typical placenta weighs about 500 g. The fetal side of the placenta is shiny because of the apposed amniotic membrane. From the fetal side, the attachment of the umbilical cord to the chorionic plate and the large placental branches of the umbilical arteries and vein radiating from it are evident. The maternal side of the placenta is dull and subdivided into as many as 35 lobes. The grooves between lobes are occupied by placental septa, which arise from the decidua basalis and extend toward the basal plate. Within a placental lobe are several cotyledons, each of which consists of a main stem villus and all its branches. The intervillous space in each lobe represents a nearly isolated compartment of the maternal circulation to the placenta.

**Umbilical Cord**

The originally broad-based body stalk elongates and becomes narrower as pregnancy progresses. The umbilical cord becomes the conduit for the umbilical vessels, which traverse its length between the fetus and the placenta (see Fig. 7-10). The umbilical vessels are embedded in a mucoid connective tissue that is often called **Wharton's jelly**.

The umbilical cord, which commonly attains a length of 50 to 60 cm by the end of pregnancy, is typically twisted many times. The twisting can be seen by gross examination of the umbilical blood vessels. In about 1% of full-term pregnancies, true knots occur in the umbilical cord. If they tighten as the result of fetal movements, they can cause anoxia and even death of the fetus.

Occasionally, an umbilical cord contains two umbilical veins if the right umbilical vein does not undergo its normal degeneration (see Fig. 17-14). Approximately 0.5% of mature umbilical cords contain only one umbilical artery. This condition is associated with a 15% to 20% incidence of associated cardiovascular defects in the fetus.
Placental Circulation

Both the fetus and the mother contribute to the placental circulation (see Fig. 7-10). The fetal circulation is contained in the system of umbilical and placental vessels. Fetal blood reaches the placenta through the two umbilical arteries, which ramify throughout the choriocnic plate. Smaller branches from these arteries enter the choriocnic villi and break up into capillary networks in the terminal branches of the choriocnic villi, where the exchange of materials with the maternal blood occurs (see Fig. 7-14). From the villous capillary beds, the blood vessels consoli-
date into successively larger venous branches. These retrace their way through the chorionic plate into the large single umbilical vein and to the fetus.

In contrast to the fetal circulation, which is totally contained within blood vessels, the maternal blood supply to the placenta is a free-flowing lake that is not bounded by vessel walls. As a result of the trophoblast’s invasive activities, roughly 80 to 100 spiral arteries of the endometrium open directly into the intervillous spaces and bathe the villi in about 150 mL of maternal blood, which is exchanged three to four times each minute.

The maternal blood enters the intervillous space under reduced pressure because of the cytotrophoblastic plugs that partially occlude the lumens of the spiral arteries. Nevertheless, the maternal blood pressure is sufficient to force the oxygenated maternal arterial blood to the bases of the villous trees at the chorionic plate (see Fig. 7-10). The overall pressure of the maternal placental blood is about 10 mm Hg in the relaxed uterus. From the chorionic plate, the blood percolates over the terminal villi as it returns to venous outflow pathways located in the decidual (maternal) plate of the placenta. An adequate flow of maternal blood to the placenta is vital to the growth and development of the fetus, and a reduced maternal blood supply to the placenta leads to a small fetus.

In the terminal (floating) villi, the fetal capillaries are located next to the trophoblastic surface to facilitate exchange between the fetal and maternal blood (Fig. 7-11). The placental barrier of the mature placenta consists of the syncytiotrophoblast, its basal lamina, the basal lamina of the fetal capillary, and the capillary endothelium. Often the two basal laminae seem to be consolidated. In younger embryos, a layer of cytotrophoblast is present in the placental barrier, but by 4 months the cytotrophoblastic layer begins to break up, and by 5 months, it is essentially gone.

**Structure of a Mature Chorionic Villus**

Mature chorionic villi constitute a very complex mass of seemingly interwoven branches (Fig. 7-12). The core of a villus consists of blood vessels and mesenchyme that is similar in composition to the mesenchyme of the umbilical cord (see Fig. 7-11). Scattered among the mesenchymal cells are large Hofbauer cells, which function as fetal macrophages.

The villus core is covered by a continuous layer of syncytiotrophoblast, with minimum numbers of cytotrophoblastic cells beneath it. The surface of the syncytiotrophoblast is covered by immense numbers of microvilli (>1 billion/cm² at term), which greatly increase the total surface area of the placenta (Fig. 7-13). The size and density of the microvilli are not constant, but change with increasing age of the placenta and differing

![Figure 7-11. Low-power transmission electron micrograph through a typical terminal villus of a human placenta. C, capillary; Ct, cytotrophoblast; S, sinusoid (dilated capillary); St, syncytiotrophoblast. (From Benirschke K, Kaufmann P: Pathology of the human placenta, ed 2, New York, 1990, Springer-Verlag.)](image-url)
environmental conditions. Under conditions of poor maternal nutrition or oxygen transport, the microvilli increase in prominence. Poor adaptation of the microvilli to adverse conditions can lead to newborns with low birth weight.

The trophoblastic surface is not homogeneous, but rather seems to be arranged into territories. Among the many functional components of the microvillous surface are (1) a wide variety of transport systems for substances ranging from ions to macromolecules, (2) hormone and growth factor receptors, (3) enzymes, and (4) numerous proteins with poorly understood functions. The placental surface is deficient or lacking in major histocompatibility antigens, the absence of which presumably plays a role in protecting against maternal immune rejection of the fetus and fetal membranes. In keeping with its active role in synthesis and transport, the syncytiotrophoblast is well supplied with a high density and a wide variety of subcellular organelles.

**PLACENTAL PHYSIOLOGY**

The transport of substances between the placenta and the maternal blood that bathes it is facilitated by the great surface area of the placenta, which expands from 5 m² at 28 weeks to almost 11 m² at term. Approximately 5% to 10% of the human placental surface consists of scattered areas where the barrier between fetal and maternal blood is extremely thin, measuring only a few microns. These areas, sometimes called **epithelial plates**, are apparently morphological adaptations designed to facilitate the diffusion of substances between the fetal and maternal circulations (Fig. 7-14).

The transfer of substances occurs both ways across the placenta. The bulk of the substances transferred from mother to fetus consists of oxygen and nutrients. The placenta represents the means for the final elimination of carbon dioxide and other fetal waste materials into the maternal circulation. Under some circumstances, other substances, some of them harmful, can be transferred across the placenta. Clinical Correlation 7-2 describes abnormal placental transfer.
Abnormal Placental Transfer

The placenta is permeable to substances that can be damaging to the embryo. Numerous maternally ingested drugs readily cross the placental barrier. Certain drugs can cause major birth defects if they reach the embryo during critical periods of morphogenesis. (Several classic examples of these are described in Chapter 8.) The placenta is highly permeable to alcohol, and excessive alcohol ingestion by the mother can produce fetal alcohol syndrome (see p. 165). Infants born addicted to heroin or crack cocaine are common in contemporary society.

In addition to drugs, certain infectious agents can penetrate the placental barrier and infect the fetus. Some (e.g., rubella virus) can cause birth defects if they infect the embryo at critical periods in development. Normally, bacteria cannot penetrate the placental barrier. Common viruses that can infect the fetus are rubella virus, cytomegalovirus, poliovirus, varicella virus, variola virus, human immunodeficiency virus, and coxsackieviruses. The spirochete Treponema pallidum, which causes syphilis, can cause devastating fetal infections. The protozoan parasite Toxoplasma gondii can cross the placental barrier and cause birth defects.

Gases, principally oxygen from the mother and carbon dioxide from the fetus, readily cross the placental barrier by diffusion. The amount of exchange is limited more by blood flow than by the efficiency of diffusion. The placenta is also permeable to carbon monoxide and many inhalational anesthetics. The latter can interfere with the transition of the newborn to independent function (e.g., breathing) if used during childbirth.

As are gases, water and electrolytes are readily transferred across the placenta. The rates of transfer are modified by colloid osmotic pressure in the case of water and the function of ion channels in the case of electrolytes. Fetal wastes (e.g., urea, creatinine, bilirubin) are rapidly transferred across the placenta from the fetal circulation to the maternal blood bathing the villi.

On the one hand, the placenta is highly permeable to certain nutrients, such as glucose, the main energy source for the fetus; on the other hand, it is considerably less permeable to fructose and several common disaccharides. Amino acids are transported across the placenta through the action of specific receptors. A certain degree of transfer of maternal free fatty acids occurs, but more must be learned about the mechanism of transfer. Vitamins, especially water-soluble ones, are transferred from the maternal to the fetal circulation.

Steroid hormones cross the placental barrier from the maternal blood. Newborn boys show evidence of the effects of exposure to maternal sex hormones. The prostatic utricle, the vestigial rudiment of the uterine primordium (fused Müllerian ducts [see Chapter 16]), is slightly enlarged in newborn boys. Conversely, female fetuses exposed to testosterone or certain synthetic progestins (especially during the 1950s and 1960s before the effects were recognized) undergo masculinization of the external genitalia. Protein hormones are, in general, poorly transported across the placenta, although symptoms of maternal diabetes may be reduced during late pregnancy because of insulin produced by the fetus. Maternal thyroid hormone gains slow access to the fetus.

Some proteins are transferred very slowly through the placenta, mainly by means of pinocytosis (uptake by membrane-bound vesicles in the cells). Of considerable importance is the transfer of maternal antibodies, mainly of the IgG class. Because of its immature immune system, the fetus produces only small amounts of antibodies. The transfer of antibodies from the mother provides a passive immunity of the newborn to certain common childhood diseases, such as smallpox, diphtheria, and measles, until the infant’s immune system begins to function more efficiently.

Small quantities of fetal blood cells often escape into the maternal circulation, either through small defects in the placental vasculature or through hemorrhage at birth. If the fetal erythrocytes are positive for the Rh antigen, and the mother is Rh negative, the presence of fetal erythrocytes in the maternal circulation can stimulate the formation of anti-Rh antibody by the immune system of the mother. The fetus in the first pregnancy is usually spared the effects of the maternal antibody (often because it has not formed in sufficient quantities), but in subsequent pregnancies, Rh-positive fetuses are attacked by the maternal anti-Rh antibodies, which make their way into the fetal bloodstream. This antibody causes hemolysis of the Rh-positive fetal erythrocytes, and the fetus develops erythroblastosis fetalis, sometimes known as hemolytic disease. In severe cases, the bilirubin released from the lysed red blood cells causes jaundice and brain damage in addition to anemia. When recognized, this condition is treated by exchange transfusions of Rh-negative donor blood into either the fetus or the newborn. An indication of the severity of this condition can be gained by examining the amniotic fluid.
Another maternal protein, transferrin, is important because, as its name implies, it carries iron to the fetus. The placental surface contains specific receptors for this protein. The iron apparently is dissociated from its transferrin carrier at the placental surface and then is actively transported into the fetal tissues.

**PLACENTAL HORMONE SYNTHESIS AND SECRETION**

The placenta, specifically the syncytiotrophoblast, is an important endocrine organ during much of pregnancy. It produces protein and steroid hormones.

The first protein hormone produced is human chorionic gonadotropin (HCG), which is responsible for maintaining the corpus luteum and its production of progesterone and estrogens. With synthesis beginning even before implantation, the presence of this hormone in maternal urine is the basis for many common tests for pregnancy. The production of HCG peaks at approximately the eighth week of gestation and then gradually declines. By the end of the first trimester, the placenta produces enough progesterone and estrogens so that pregnancy can be maintained even if the corpus luteum is surgically removed. The placenta can independently synthesize progesterone from acetate or cholesterol precursors, but it does not contain the complete enzymatic apparatus for the synthesis of estrogens. For estrogen to be synthesized, the placenta must operate in concert with the fetal adrenal gland and possibly the liver; these structures possess the enzymes that the placenta lacks.

Another placental protein hormone is chorionic somatomammotropin, sometimes called human placental lactogen. Similar in structure to human growth hormone, it influences growth, lactation, and lipid and carbohydrate metabolism. The placenta also produces small amounts of chorionic thyrotropin and chorionic corticotropin. When they are secreted into the maternal bloodstream, some placental hormones stimulate changes in the metabolism and cardiovascular function of the mother. These changes ensure that appropriate types and amounts of fundamental nutrients and substrates reach the placenta for transport to the fetus.

A good example of a placental hormone that influences the mother is human placental growth hormone. This hormone, which differs by 13 amino acids from pituitary growth hormone, is produced by the syncytiotrophoblast. Placental growth hormone is not detectable in fetal serum, although it seems to influence growth of the placenta in a paracrine manner. This fetal hormone exerts a profound effect on the mother. During the first 15 to 20 weeks of pregnancy, maternal pituitary growth hormone is the main form present in the maternal circulation, but from 15 weeks to term, placental growth hormone gradually replaces maternal pituitary growth hormone to the extent that the maternally derived hormone becomes undetectable in the mother’s serum. A major function of this hormone seems to be the regulation of maternal blood glucose levels so that the fetus is ensured of an adequate nutrient supply. Placental growth hormone secretion is stimulated by low maternal glucose levels. The increased hormone levels then stimulate gluconeogenesis in the maternal liver and other organs, increasing the supply of glucose available for fetal use.

In certain respects, the placenta duplicates the multilevel control system that regulates hormone production in the postnatal body. Cells of the cytotrophoblast produce a homologue of gonadotropin-releasing hormone (GnRH), as is normally done by the hypothalamus. GnRH passes into the syncytiotrophoblast, where it, along with certain opiate peptides and their receptors (which have been identified in the syncytiotrophoblast), stimulates the release of HCG from the syncytiotrophoblast. The opiate peptides and their receptors are also involved in the release of chorionic somatomammotropin from the syncytiotrophoblast. Finally, HCG seems to be involved in regulating the synthesis and release of placental steroids from the syncytiotrophoblast.

In addition to hormones, the placenta produces a wide variety of other proteins that have principally been identified immunologically. The functions of many of the placental proteins that have been discovered are still very poorly understood.

**PLACENTAL IMMUNOLOGY**

One of the major mysteries of pregnancy is why the fetus and placenta, which are immunologically distinct from the mother, are not recognized as foreign tissue and rejected by the mother’s immune system. (Immune rejection of foreign tissues normally occurs by the activation of cytotoxic lymphocytes, but humoral immune responses are also possible.) Despite considerable research, the answer to this question is still unknown. Several broad explanations have been suggested to account for the unusual tolerance of the mother to the prolonged presence of the immunologically foreign embryo during pregnancy.

The first possibility is that the fetal tissues, especially those of the placenta, which constitute the direct interface between fetus and mother, do not present foreign antigens to the mother’s immune system. To some extent, this hypothesis is true because neither the syncytiotrophoblast nor the nonvillous cytotrophoblast (cytotrophoblastic shell) expresses the two major classes of major histocompatibility antigens that trigger the immune response of the host in the rejection of typical foreign tissue grafts (e.g., a kidney transplant). These antigens are present, however, on cells of the fetus and in stromal tissues of the placenta. The expression of minor histocompatibility antigens (e.g., the HY antigen in male
Placental Pathological Conditions

Placental pathological conditions cover a wide spectrum, ranging from the abnormalities of implantation site to neoplasia to frank bacterial infections. Much can be learned about the past history and future prospects of a newborn by examining the placenta. This box deals only with the aspects of placental pathology that are relevant to developmental mechanisms.

Abnormal Implantation Sites

An abnormal implantation site within the uterine cavity is known as placenta previa. (Ectopic pregnancy is covered in Chapter 3.) When part of the placenta covers the cervical outlet of the uterine cavity, its presence is a mechanical obstacle in the birth canal. In addition, hemorrhage, which can be fatal to the fetus or the mother, is a common consequence of placenta previa as a result of the premature separation of part of the placenta from the uterus.

Gross Placental Anomalies

Many variations in shape of the placenta have been described, but few seem to be of any functional significance. One involves marginal rather than central attachment of the umbilical cord (Fig. 7-15A). If the umbilical cord attaches to the smooth membranes outside the boundaries of the placenta itself, the condition is known as a velamentous insertion of the umbilical cord (Fig. 7-15B). The placenta itself can be subdivided into accessory lobes (Fig. 7-15C). It can also be completely divided into two parts, with smooth membrane between (Fig. 7-15D).

Hydatidiform Mole

A hydatidiform mole is a noninvasive condition in which many of the chorionic villi are characterized by nodular swellings, giving them an appearance similar to bunches of grapes. Commonly, much of the villous surface of the placenta takes on this appearance; in addition, the

Continued
embryo is either absent or not viable (Fig. 7-16). The villi show no evidence of vascularization.

Genetic analysis has determined that hydatidiform moles represent the results of paternal imprinting where the female pronucleus of the egg does not participate in development (see Chapter 3). Instead, the chromosomal material is derived from two sperm that had penetrated the egg or by duplication of a single sperm pronucleus within the egg. The chromosomes of hydatidiform moles are paternally derived 46,XX because the number of lethal genes in 46,YY embryos is not compatible with tissue survival.

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PLACENTA AND MEMBRANES IN MULTIPLE PREGNANCIES

Several different configurations of the placenta and extra-embryonic membranes are possible in multiple pregnancies. Dizygotic twins or monozygotic twins resulting from complete separation of blastomeres very early in cleavage can have completely separate placentas and membranes if the two embryos implant in distant sites on the uterine wall (Fig. 7-17A). In contrast, if the implantation sites are closer together, the placentas and chorions (which were initially separate at implantation) can fuse, although the vascular systems of the two embryos remain separate (Fig. 7-17B).

When monozygotic twins form by splitting of the inner cell mass in the blastocyst, it is usual to have a common placenta and a common chorion, but inside the chorion the twin embryos each develop within separate amnions (Fig. 7-17C). In this case, there can be separate or fused vascular systems within the common placenta. When the vascular systems are fused, one twin may receive a greater proportion of the placental blood flow than the other. This situation may result in mild to severe stunting of growth of the embryo that receives the lesser amount of blood from the placenta. The twin from which the blood is siphoned is often highly misshapen and is commonly called an acardiac monster (Fig. 7-18).

In conjoined twins and rarely in dizygotic twins with minimal separation of the inner cell mass, the embryos develop within a single amnion and chorion and have a common placenta with a common blood supply (Fig. 7-17D and E). This and the previously described conditions can be determined by examination of the membranes of the afterbirth. It was previously thought that it could be determined whether twins were monozygotic or dizygotic by simple examination of the membranes. Although in most cases the correct inference can be made, this method is not foolproof. Other methods, ranging from simple observation of gender, eye color, and finger-
print patterns to determination of blood types or even DNA fingerprinting, should be used for a definitive determination. In the current age of organ and cell transplantation, it can be vital to know whether twins are monozygotic in the event that one develops a condition that can be treated by a transplant.

**CLINICAL VIGNETTE**

A 32-year-old woman's obstetrician notes that her weight gain during late pregnancy is excessive. At least part of her weight gain seems to be the result of a greater-than-normal volume of amniotic fluid. She lives in a remote rural area far from an imaging center. Amniocentesis is performed, and the laboratory report indicates the presence of a high level of α-fetoprotein in the amniotic fluid. The obstetrician is concerned that this pregnancy will not result in a normal single birth.

What condition does the obstetrician suspect and why?
A. Esophageal atresia
B. Renal agenesis
C. Triplets
D. Anencephaly
E. Placenta previa

**SUMMARY**

- The extraembryonic membranes consist of the chorion (the combination of trophoblast plus underlying extraembryonic mesoderm), amnion, yolk sac, and allantois.

- The amnion, a thin ectodermal membrane lined with mesoderm, grows to enclose the embryo like a balloon. It is filled with a clear fluid, which is generated from many sources, such as the fetal skin, the amnion itself, the fetal kidneys, and possibly the fetal vessels. At term, the volume of amniotic fluid approaches 1 L. Amniotic fluid is removed by exchange across the amniotic membrane and by fetal swallowing.

- The yolk sac is a ventral, endodermally lined structure that does not serve a nutritive function in mammalian embryos. Mesodermal blood islands in the wall of the yolk sac form the first blood cells and vessels. Primordial germ cells are recognizable in the wall of the yolk sac, but they originate in extraembryonic mesoderm at the base of the allantois.

- The allantois is a small, endodermally lined diverticulum off the ventral side of the hindgut. It does not serve a direct function of respiration or storage of wastes in humans. These functions are carried out through the placenta and the umbilical vessels that arise in conjunction with the allantois.

- Chorionic villi form as outward projections from the trophoblast. Primary villi consist of projections of trophoblast alone. When a mesenchymal core forms within a villus, it is a secondary villus, and when the mesenchyme becomes vascularized, the villus is a tertiary villus. As villi mature, the cytrophoblast in some villi grows through the syncytiotrophoblast as cytotrophoblastic cell columns and makes contact with the maternal endometrial tissue. Cytotrophoblast continues to grow around the blood-filled space surrounding the chorion to form a cytotrophoblastic shell, which is the direct interface between the fetal and maternal tissues. Villi that make direct contact with maternal tissues are anchoring villi; villi that do not make such contact are floating villi. Because chorionic villi float in a pool of maternal blood, the human placenta is designated as a hemochorial placenta.

- Stimulated by the implanting embryo, endometrial stromal cells undergo the decidual reaction. Maternal tissues that are lost at childbirth are, collectively, the decidua. The decidua basalis underlies the placenta; the decidua capsularis encircles the remainder of the chorion like a capsule; portions of the uterine wall not occupied by the fetal chorion are the decidua parietalis. As the fetal chorion matures, it becomes subdivided into a chorion laeve, in which the villi regress, and the chorion frondosum, which is the region of chorion nearest the basal tissues of the endometrium. The chorion frondosum ultimately develops into the placenta.
The mature placenta consists of the wall of the chorion (the chorionic plate) and numerous villi protruding from it. The fetal surface of the placenta is smooth and shiny because of the apposed amniotic membrane. The maternal surface is dull and lobulated, with cotyledons of numerous placental villi and their branches. The umbilical cord (formerly the body stalk) enters the middle of the placenta. Blood from the fetus reaches the placenta via the umbilical arteries. These branch out into numerous small vessels, terminating into capillary loops in the ends of the placental villi. There, oxygen, nutrients, and wastes are exchanged between fetal and maternal blood, which bathes the villi. Fetal blood returns to the body of the mature fetus via a single umbilical vein. Maternal blood exiting open-ended spiral arteries of the endometrium bathes the placental villi.

The transfer of substances from fetal to maternal blood must occur across the endothelium of the fetal capillaries, a basal lamina, and trophoblastic tissues before reaching the maternal blood. The transfer of substances is accomplished by passive and active mechanisms. In addition to normal substances, alcohol, certain drugs, and some infectious agents can pass from the maternal blood into the fetal circulation and interfere with normal development. If a fetus is Rh positive and the mother is Rh negative, maternal anti-Rh antibodies from a previous pregnancy can pass to the fetus to cause erythroblastosis fetalis.

The placenta produces a wide variety of hormones, many of which are normally synthesized in the hypothalamus and anterior pituitary gland. The first hormone released is HCG, which serves as the basis of many pregnancy tests. Other placental hormones are chorionic somatomammotropin (human placental lactogen), steroid hormones, human placental growth hormone, and chorionic thyrotropin and corticotropin.

The fetal and placental tissues are immunologically different from those of the mother, but the placenta and fetus are not immunologically rejected. The reason is still unclear, but some explanations involve reduced antigenicity of the trophoblastic tissues, paralysis of the mother’s immune system during pregnancy, and local immunological barriers between the fetus and mother.

The placenta is delivered about 30 minutes after the fetus as the afterbirth. Inspection of the placenta can reveal placental pathological conditions, missing cotyledons, or the arrangement of membranes in multiple pregnancies. The last finding can help to determine whether a multiple birth is monozygotic in origin. Placental pathological findings include abnormal gross shape, benign hydatidiform moles, and malignant choriocarcinomas.

**REVIEW QUESTIONS**

1. In the mature placenta, which fetal tissue directly interfaces with the maternal uterine connective tissue?
   A. Cytotrophoblast
   B. Syncytiotrophoblast
   C. Extraembryonic mesoderm
   D. Decidual cells
   E. None of the above

2. Which condition is related to paternal imprinting?
   A. Accessory placental lobes
   B. Placenta previa
   C. Oligohydramnios
   D. Single umbilical artery
   E. Hydatidiform mole

3. Blood vessels associated with which structure enter the fetal component of the placenta?
   A. Decidua basalis
   B. Allantois
   C. Amnion
   D. Yolk sac
   E. Decidua parietalis

4. What type of cells invades the maternal spiral arteries and reduces the flow of blood from their open ends?
   A. Hofbauer cells
   B. Syncytiotrophoblast
   C. Fetal erythrocytes
   D. Cytotrophoblast
   E. Amniotic epithelium

5. Which condition of the extraembryonic membranes can be found in uteri containing identical twins?
   A. Common placenta and amniotic membrane
   B. Common placenta and chorion, separate amnions
   C. Separate placentas and extraembryonic membranes
   D. Common placenta, partially fused chorions
   E. All of the above

6. A 28-year-old Rh-negative woman’s second son is born severely jaundiced. Which characteristic most likely describes her first child?
   A. Male
   B. Female
   C. Rh positive
   D. Rh negative
   E. Hydramnios

7. Why is the human placenta designated a hemochorial type of placenta?
8. Through what layers of a placental villus must a molecule of oxygen pass to go from the maternal blood into the embryonic circulation?

9. What embryonic hormone has served as the basis for many standard pregnancy tests and why?

10. Why must a pregnant woman be very careful of what she eats and drinks?

REFERENCES

Naeye RL: Disorders of the placenta, fetus, and neonate, St Louis, 1992, Mosby.