1 PLACENTAL DEVELOPMENT AND ANATOMY

Understanding a little about the development of the placenta helps the pathologist interpret findings, especially those that are affected by gestational age. There is a wealth of recent information about placental development and its molecular controls, and we refer the interested reader to those for a more in depth study (1–4). In this brief overview, we focus on a morphologic description of placental development as applicable to the interpretation of placental pathology.

EARLY PLACENTAL DEVELOPMENT: TROPHOBLAST DIFFERENTIATION AND IMPLANTATION

The human placenta develops from the shell of trophectoderm surrounding the embryonic disc/inner cell mass (fig. 1-1). The trophectoderm is the precursor to all the trophoblast lineage, including the villous trophoblast and the extravillous trophoblast. The trophectoderm is the first differentiated cell type to form in the zygote, defined molecularly at the compact blastocyst stage at about day 3 to 4 postfertilization (dpf) (5).

At the blastocyst stage the trophectoderm is a spherical shell around the embryonic disc and has a polarity related to its proximity to the embryo. The blastocyst implants into the uterus at about 7dpf so that the embryonic pole is deep to the endometrial cavity (fig. 1-2). Once enmeshed in the decidua, the trophectoderm shell focally differentiates into a specialized tissue called the primitive syncytium, which invades into the decidua to start the complete implantation process (6). The blastocyst becomes completely encased in the decidualized endometrium around 9 dpf. The portion of decidua lying between blastocyst and myometrium is the decidua basalis; the portion covering superficial trophectoderm is the decidua capsularis (fig. 1-2).

The trophoblastic syncytium develops clefts (lacunae) that coalesce to form the most primitive type of the future intervillous space (fig. 1-3). During this time, the trophectoderm gives rise to the cytotrophoblast (CT), a cell that will persist throughout gestation as the precursor trophoblast cell to its progeny, differentiated and specialized cells, the syncytiotrophoblast (ST) and the extravillous trophoblast (EVT). The terminally differentiated ST is a true syncytial epithelium that has many important transport and barrier functions in the placenta. The EVT
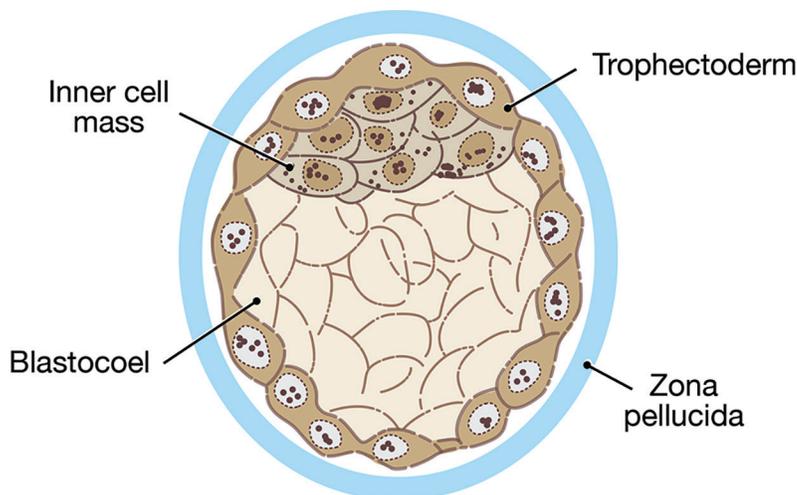

Figure 1-1

BLASTOCYST

Depiction of a blastocyst showing the trophectoderm surrounding the inner cell mass. (Adapted with permission from fig. 3.1 from Carlson BM. Human embryology and developmental biology, 5th ed. Philadelphia: Saunders/Elsevier; 2014.)
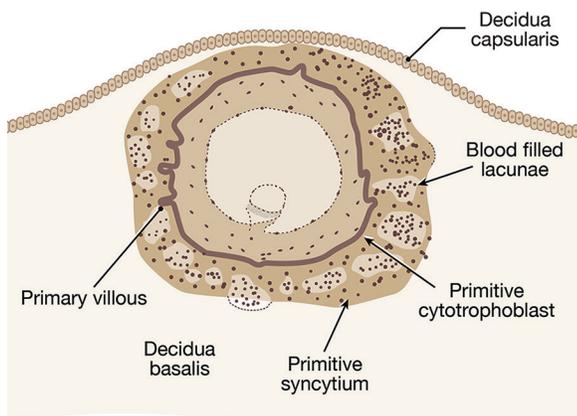
Figure 1-2

BLASTOCYST

Depiction of an implanted blastocyst with the deep embryonic pole. The decidua deep to the embryonic pole is the decidua basalis; that around the superficial is the decidua capsularis.
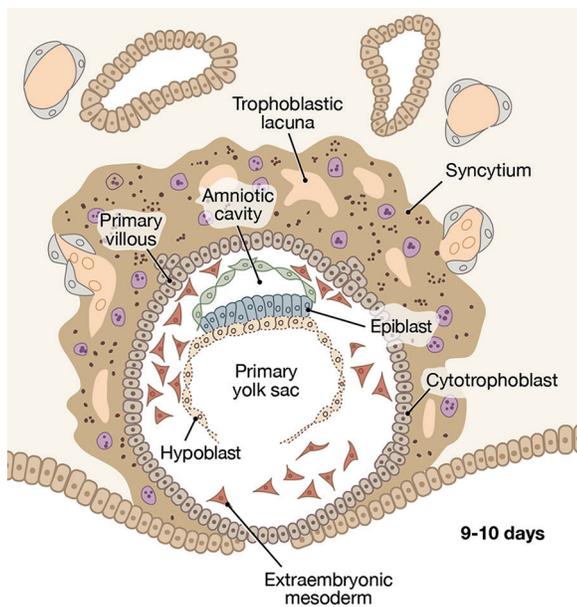

Figure 1-3

BLASTOCYST

Depiction of the implanted blastocyst with growing trophectoderm forming lacunae (primitive intervillous space).

has at least two lineages, interstitial EVT (iEVT) and endovascular EVT (eEVT), which play different roles in the implantation process (7).

The CT remains in the chorion and villi of the placenta proper as the "stem cell" of the tro-
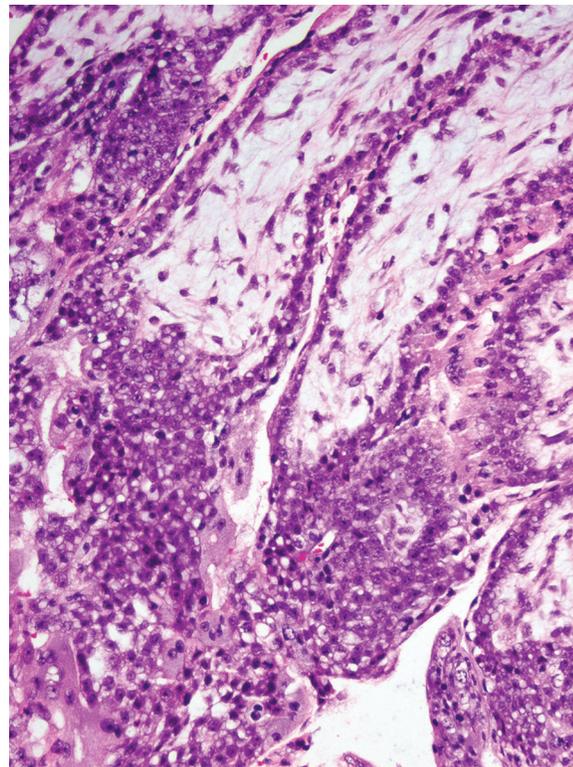

Figure 1-4

EARLY VILLUS

Early villus with polarized trophoblast growing in a cell column.

phoblastic lineage. In the villi, the CT is present immediately subjacent to the villous ST and can differentiate and fuse with the ST for growth and renewal of the ST layer. Cell columns of CT connect the anchoring villi to the basal plate (fig. 1-4); the iEVT and eEVT differentiate from them at the decidual interface. The morphology of the trophoblast lineage and immunoprofile are described in Table 1-1.

Implantation is a complex event coordinated by the interaction of the trophoblast, decidua, and decidual inflammatory cells. Both the iEVT and eEVT play critical roles in the implantation process (3). eEVT cells enter the maternal arterioles and penetrate deeply along their endothelial linings. This endovascular growth results in obstruction of the maternal vessels, leading to low oxygen concentrations in the developing embryo. These eEVT plugs are essential for normal human placentogenesis and embryogenesis (fig. 1-5). Hustin et al. (8) offered evidence that the eEVT

	Table 1-1	
	TROPHOBLAST PHENOTYPE	
Trophoblast	**Morphology**	**Immunophenotype**
Cytotrophoblast	Medium-sized round to cuboidal cells with central vesicular nuclei; distinct cell borders	AE1/AE3, CK7, CK18+ hCG– p63+ Ki-67+ HLA-G–
Extravillous trophoblast: interstitial and endovascular	Large polyhedral to spindled cells with dense purple cytoplasm; mononuclear to binucleate; often have pseudonuclear inclusions; occasionally multinucleate but retaining large nuclei in contrast to syncytiotrophoblastic small nuclei; indistinct cell borders	AEI/AE3, CK7, CK18+ hPL+ Focally weakly hCG+ HLA-G+ Inhibin+ p63– melCAM+ PD-L1+
Syncytiotrophoblast	Large cells with multiple small dark nuclei and densely eosinophilic cytoplasm	AE1/AE3, CK7, CK18+ hPL+ Strongly hCG+ Inhibin+ HLA-G– p63– melCAM– PD-L1+

cells completely occlude the vessels in early pregnancy, thus allowing only a filtrate of maternal blood to "perfuse" the developing placenta and zygote. This process is critical in human development and if it does not happen appropriately, pregnancy failure results (9,10). Any significant blood flow to the placenta does not occur until approximately 10 to 12 weeks gestation (11,12). Nutritional support for the developing conceptus comes from transudates and also from glandular secretions (13), histiotrophic transfusions, direct continuity of the syncytium to endometrial glands (12,14), and later perhaps by direct invasion of glands by EVT (15).

As the eEVT performs this process, the iEVT invades the decidua usually as isolated cells or columns of cells, homing toward the spiral arteries to invade and replace their vascular muscular wall with fibrinoid material. iEVT also invades decidual veins and lymphatics (16). Both the iEVT and eEVT play roles in remodeling the spiral arteries/arterioles from muscularized high-pressure vessels to static high-capacitance low-pressure vessels by 10 to 12 weeks' gestational age (2). The end result of EVT uteroplacental artery remodeling is the apparent replacement of the vascular endothelium and smooth muscle by
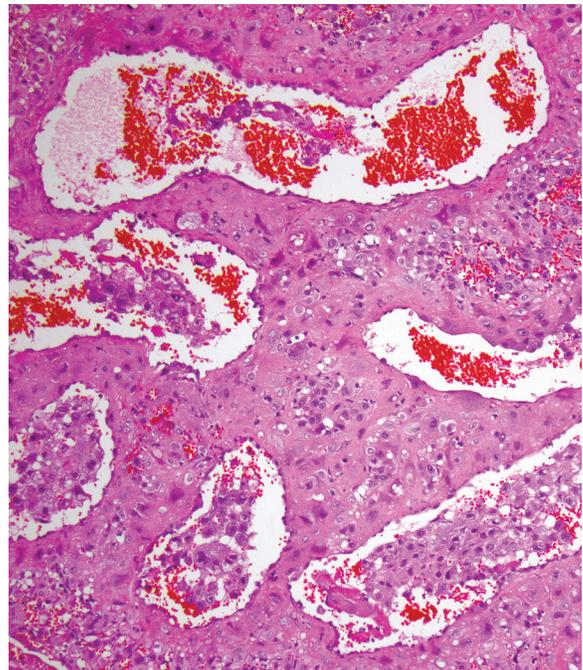

Figure 1-5

IMPLANTATION SITE

Implantation site with endovascular extravillous trophoblast (eEVT) plugs in the decidual vessels.
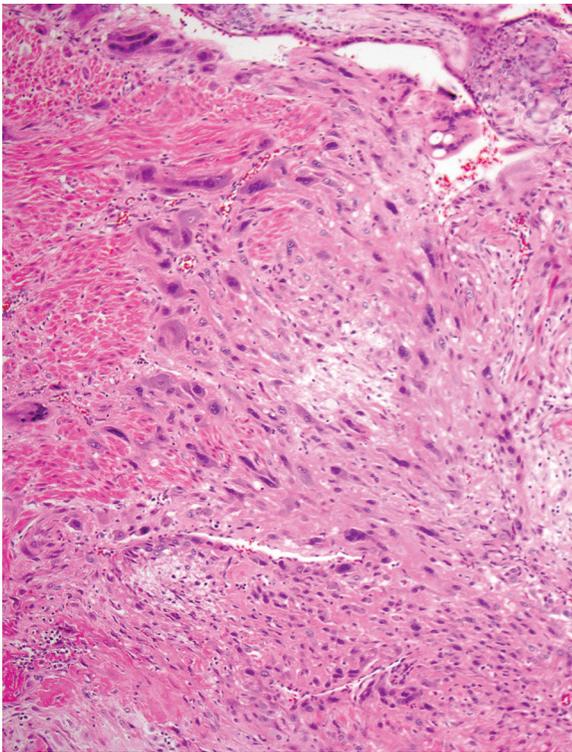
Figure 1-6

IMPLANTATION SITE

Implantation site at the decidual-myometrial border showing abundant interstitial EVT (iEVT), some forming giant cells.

Figure 1-7

SPIRAL ARTERIOLE

Remodeled spiral arteriole in the implantation site.

trophoblast, with loss of vascular wall elasticity and loss of vasomotor control (17). iEVT cells infiltrate the decidua and myometrium, often fusing to form placental giant cells (fig. 1-6). This process continues through about 20 weeks' gestation and deep to the inner third of the myometrial portion of the spiral arteries (18,19).

The iEVT cells are embedded in self-secreted extracellular matrix (fibrinoid) and additionally express extracellular matrix receptors, the integrins. Integrins interact with the vascular wall matrices, decidual natural killer cells (dNK), decidual macrophages, and other cell types in accomplishing the task of trophoblast invasion. In addition, matrix metaloproteinases (MMPs) of several types help in the destruction of decidua, iEVT invasion of maternal spiral arterioles, and destruction of their vascular walls. The result is a remodeled spiral artery in which the muscular wall is replaced by fibrin and trophoblast (fig. 1-7). The invasion process must be
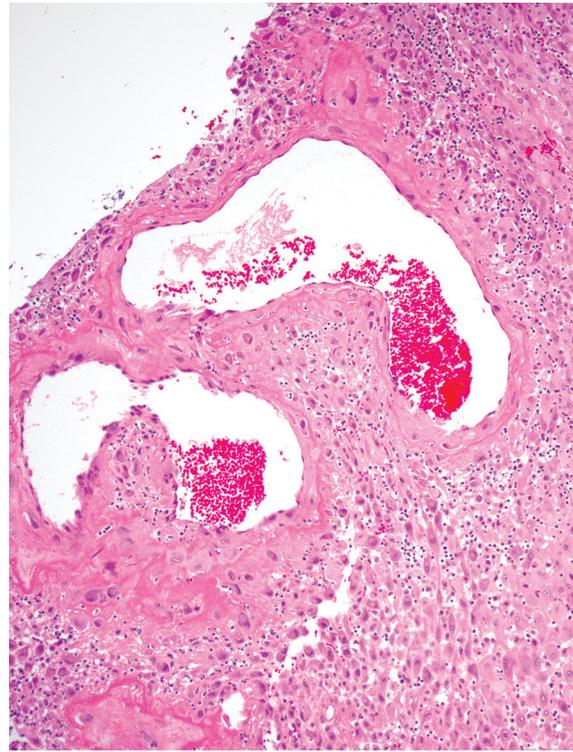
tightly regulated and decidua, myometrium, and dNK cells all play roles in directing and limiting this process (20,21).

EVTs must evade maternal rejection as they are semiallografts. They do this, in part, by expressing a specialized set of human leukocyte antigen (HLA) proteins to modulate the maternal immunologic response. These nonclassic HLA factors include HLA-G, as well as HLA-C and -E (22–24). The trophoblast does not express HLA-A or -B. HLA-G helps the EVT avoid the rejection response by promoting immunotolerance at the maternal interface. HLA-G is often used as a marker of the EVT lineage.

Abnormal implantation is thought to cause placental pathologies (e.g., fetal growth restriction and preeclampsia) (25,26), and early pregnancy loss (9,10). It is believed that this process of EVT and vascular remodeling is abnormal and shallow in preterm preeclampsia and is the cause of the oxidative stress to the trophoblast and developing placenta (see chapter 9-3).
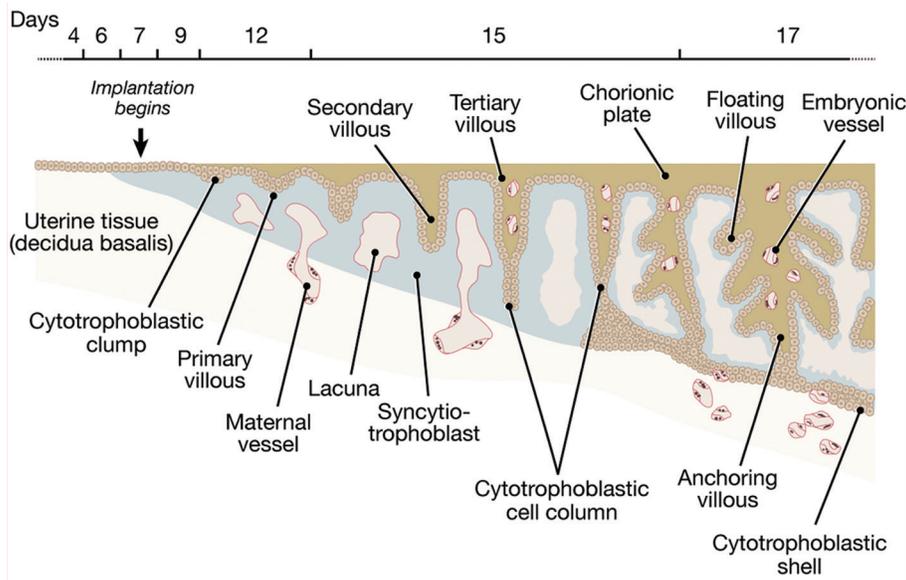
Figure 1-8

VILLOUS PROGRESSION

Depiction of villous progression from primary to tertiary villi. (Adapted with permission from fig. 7.4 from Carlson BM. Human embryology and developmental biology, 5th ed. Philadelphia: Saunders/Elsevier; 2014.)

LATER PLACENTAL DEVELOPMENT: DISC FORMATION

During the implantation process by the EVT, the placental disc begins to form. Early placentas are composed entirely of epithelial cells: the CT and the ST. The placenta begins to form as the CT forms columns surrounded by ST, the primary villus (fig. 1-8). At around 13 dpf, extraembryonic mesoderm invades the primary villi to form secondary villi (fig. 1-8). At first, villi form all around the developing embryo in a sphere, but early on in human placentation, the placental disc is formed by atrophy of the lateral villi and anti-embryonic pole villi, which will form the margins of the placenta and the chorion laeve (fig. 1-9).

Placental vascular development is a process of angiogenesis and vasculogenesis regulated by signals from the villous CT. Hemangioblasts in the villous stroma respond by forming the early villous vessels. The villous capillaries form at around 18 to 20 dpf. These villous vessels coalesce and connect to the omphalomesenteric, and later, to allantoic vessels of the embryonic body stalk. True fetal circulation is active earliest at 21 dpf, long before the maternal-placental perfusion occurs at 10 to 12 weeks' gestational age. The initial fetal blood cells are yolk sac derived and only after the 2nd month do they issue from fetal hematopoietic cells in the liver and later still from the bone marrow. With an established circulation, the villi are now called tertiary villi (fig. 1-8).
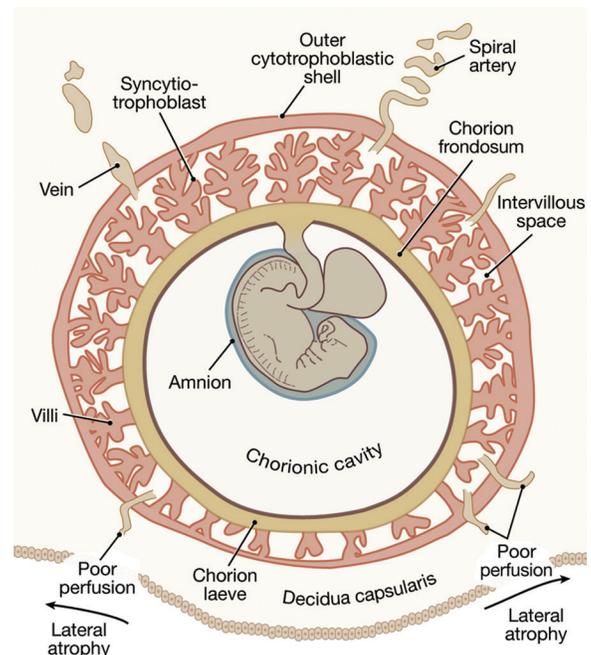

Figure 1-9

FORMATION OF THE PLACENTAL DISC

With villous formation and continued expansion of the membranes, there is lateral atrophy of the placenta due to relatively poorer maternal perfusion at the margins. (Adapted with permission from fig. 7.5 from Carlson BM. Human embryology and developmental biology, 5th ed. Philadelphia: Saunders/Elsevier; 2014.)
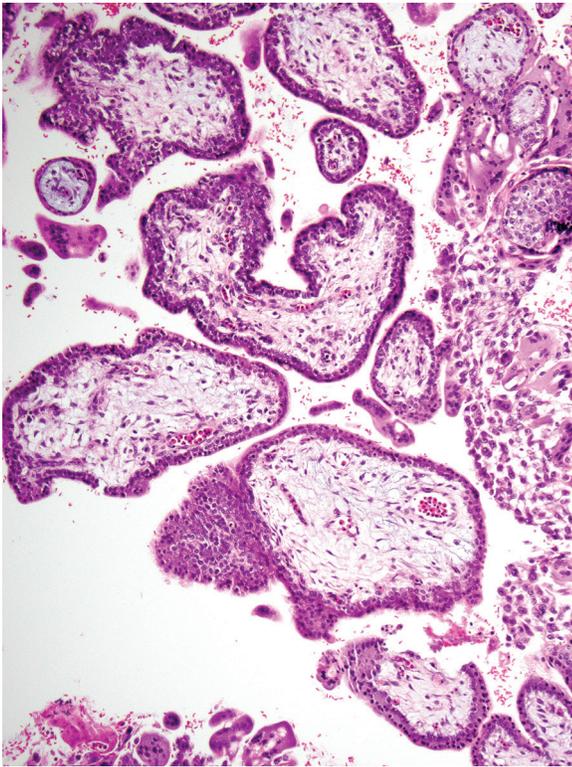
Figure 1-10

FIRST TRIMESTER VILLI

First trimester villi demonstrate open villous stroma, two trophoblastic layers around the villi, and nucleated fetal red blood cells.

Figure 1-11

SECOND TRIMESTER VILLI

Second trimester villi show denser villous stroma, two layers of trophoblast around the villus, and circulating predominantly anucleate fetal red blood cells.

After the formation of the discoid placenta and tertiary villi, the eEVTs degrade and maternal perfusion of the placenta ensues. The placenta as an organ is now responsible for gas and nutrient exchange, and continued hormone production, synthesis, and release of other factors critical in maintaining the viability of the placental/embryo unit as it develops. Much of this work belongs to the villous ST; viability of the ST is thus critical for normal human development.

The villous morphology changes appreciably during gestation (27), and the gestational age can be crudely estimated from the histologic appearance of the villi. In first and early second trimester placentas, the mesenchymal core of the villus is extremely loosely structured, appearing almost edematous (fig. 1-10) since the villi are primarily mesenchymal and immature intermediate villi. The surface is uniformly covered by an inner layer of cellular, mitotically active CT, and
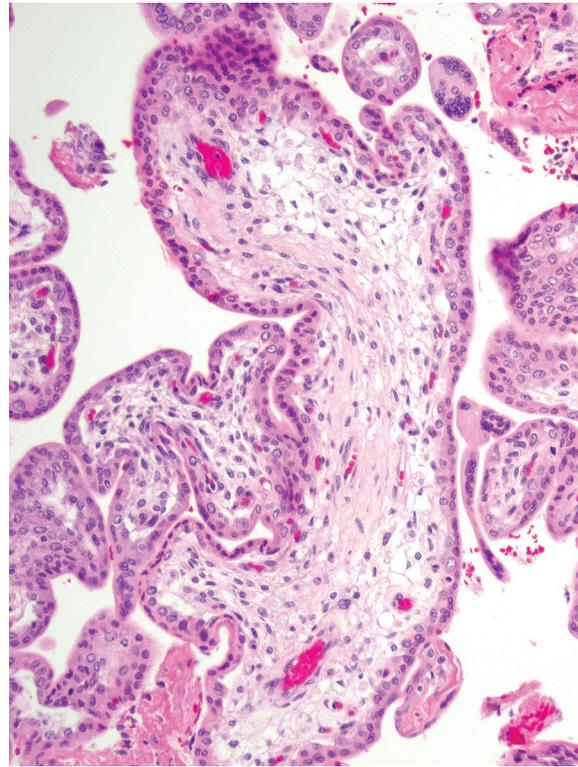
superficially by a thick layer of ST (two trophoblastic cell layers surround the villous stroma). Capillaries are filled with nucleated hematopoietic cells and lie close to the villous surface, separated from the maternal vascular space (the intervillous space) by at least three cellular layers: the endothelium, CT, and ST (fig. 1-11).

In the second trimester, the villi elongate, lose their central edema, branch successively, and decrease in diameter. These are the mature intermediate villi (fig. 1-12). The stroma becomes denser and the capillaries peripheralize to the surface of the villi. Second trimester villi still have two cell layers of trophoblast surrounding the villi but the CT layer starts to become less evident in the later part of the second trimester.

In the third trimester, CT are somewhat difficult to find, yet still present (fig. 1-13). Although CT mitoses are identifiable in the first and second trimester, they are rare after
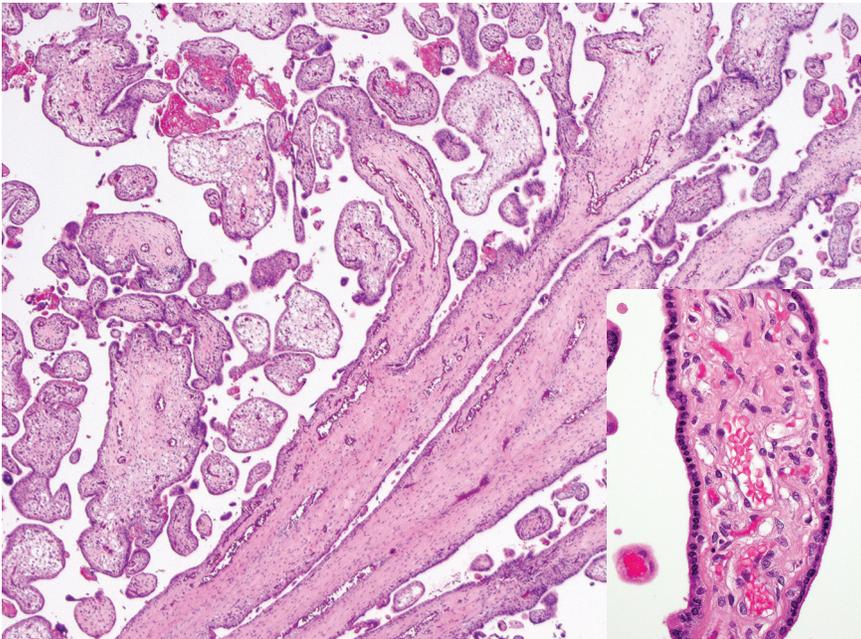
Figure 1-12

MATURE INTERMEDIATE VILLUS

Mature intermediate villus from a third trimester placenta shows a dense stromal core, peripheralized vessels, and paucity of cytotrophoblast. Inset shows higher-power view of a different intermediate villus to show the trophoblast with paucity of cytotyrophoblast.
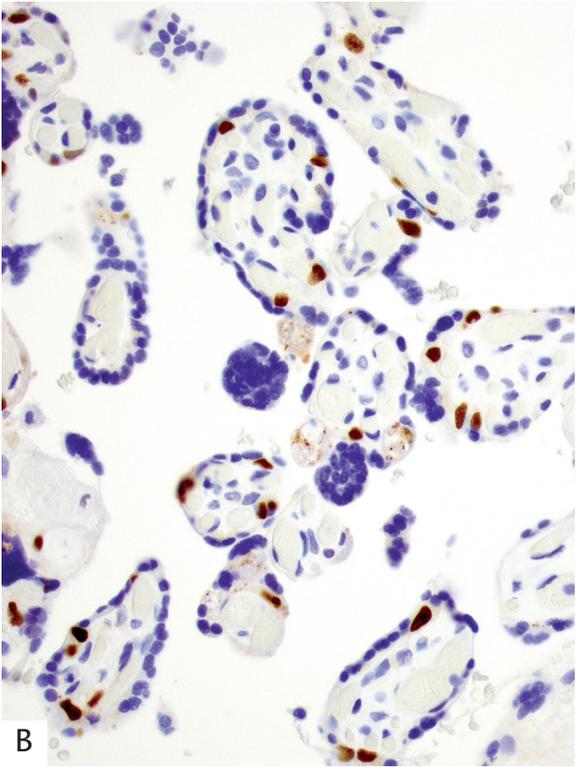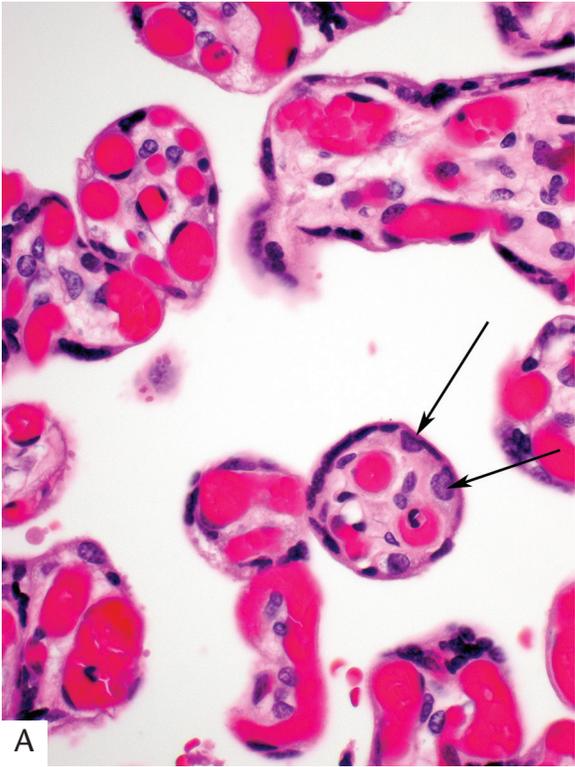

Figure 1-13

TERTIARY VILLI

A: Tertiary villi from a term placenta show scant cytotrophoblast (arrows).
B: A different case of term tertiary villi with cytotrophoblast highlighted by the p63 stain.
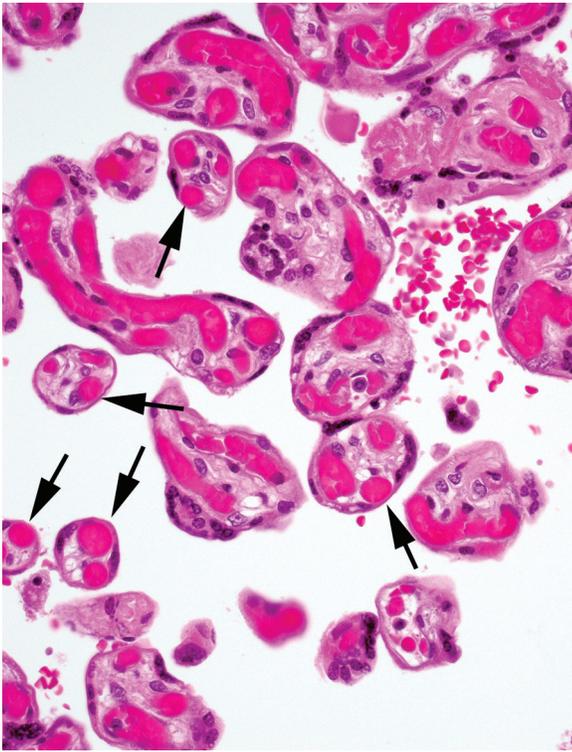
Figure 1-14

VASCULOSYNCYTIAL MEMBRANES

Vasculosyncytial membranes in a term placenta (arrows). A single thin layer of membranes separates the maternal from the fetal vascular spaces.
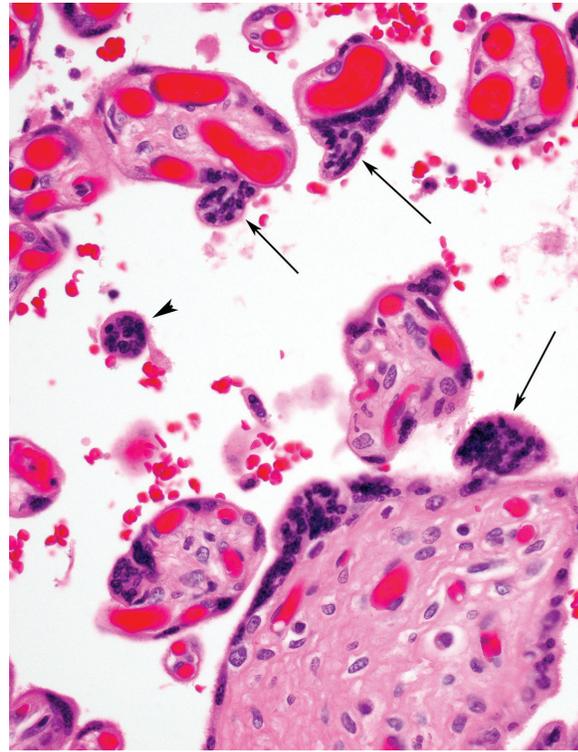

Figure 1-15

SYNCYTIOTROPHOBLASTIC KNOTS

Syncytiotrophoblastic knots are seen (arrows). An arrowhead points to a free knot.

36 weeks in normal placentas. From the mature intermediate villi, the terminal villi bud and branch. Usually by the third trimester terminal villi predominate. Terminal villi contain little stroma and are filled with distended looped capillaries. In the mature terminal villus, the fetal blood is separated from the maternal space by one nearly fused layer of capillary endothelium and ST, the vascular syncytial membrane (fig. 1-14). This structure is the definition of a mature villus, should be easily identified in the terminal villi in the third trimester, and should dominate by term. Abnormalities in villous maturation, either accelerated or delayed, are associated with fetal morbidity and mortality (see chapter 8-2).

The chorionic villi are made up of stroma and vessels surrounded by trophoblast. They have resident macrophages, called Hofbauer cells, which are more prominent in preterm than term placentas. Most believe that there are no lymphatics in the villi, but recently new lymphatic markers have shown that it may be that villous lymphatic channels do exist (28,29).

The mature placental senescent ST form "knots" (fig. 1-15), many of which break loose and are swept into the intervillous circulation, which takes them to the maternal lung, where they are destroyed by apoptosis. ST knots are present at term in less than 30 percent of the terminal villi (30); more than that is a feature of maternal vascular malperfusion (MVM) (31) and has been termed "Tenney-Parker change" (32) (see chapter 8-3). Less than that may be a feature of delayed villous maturation. Normally knots contain less than 10 jumbled nuclei; more that are described as large knots and are usually seen in MVM. ST knots are inert senescent ST nuclei (33), and they are presumably the source of the large quantities of "cell-free DNA" in the maternal circulation that is now used for fetal genotyping (34). They are not to be confused with ST sprouts, which are paddle-like

outgrowths of ST in the formation of new villi. These are broader growths with less crowded, more open appearing nuclei and are transcriptionally active (fig. 1-16) (33). ST bridges are structures of true ST fusions of adjacent villi due to longstanding villous crowding, and are a feature of villous agglutination (fig. 1-17) (35).

The placental disc is made up of lobules or units of villi, often termed cotyledons. The average placenta contains between 3 and 37 lobules (36). They can be seen from the basal plate (fig. 1-18). The umbilical arteries branch on the surface of the chorionic plate (chorion frondosum) and traverse over the plate to perfuse a lobule or lobules. An accompanying chorionic vein returns oxygenated blood back to the umbilical vein and then to the fetus. The chorionic arteries traverse on top of the veins, and with careful inspection, pairs are seen as they "dive down" or "come up" from/to their lobules (fig. 1-19). There are about 120 maternal spiral arteries perfusing these 3 to 37 lobules.

The pattern of the chorionic plate vessels varies. Generally, the vessels branch at the umbilical cord insertion in either a dispersal/dichotomous (fig. 1-20) or a magistral/monopodial pattern (fig. 1-21). In the dispersal/dichotomous type, the umbilical vessels undergo successive divisions of gradually diminishing caliber toward the periphery, while in the magistral/monopodial pattern the vessels traverse to the edge of the placenta with daughter smaller
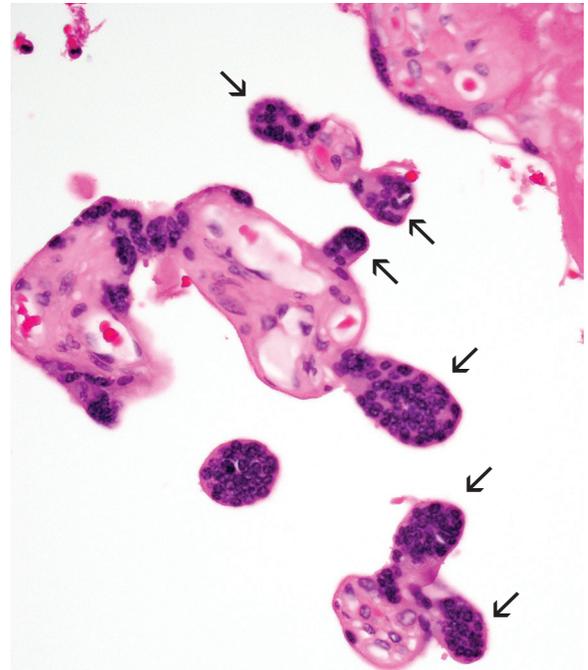

Figure 1-16

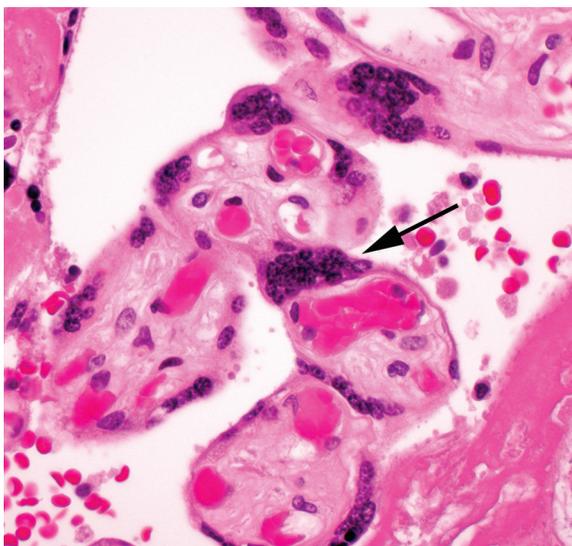**SYNCYTIOTROPHOBLASTIC SPROUTS**

Arrows indicate the sprouts.

Figure 1-17

SYNCYTIOTROPHOBLASTIC BRIDGE

An arrow points to a bridge.

Figure 1-18

MATERNAL FLOOR FROM A TERM PLACENTA

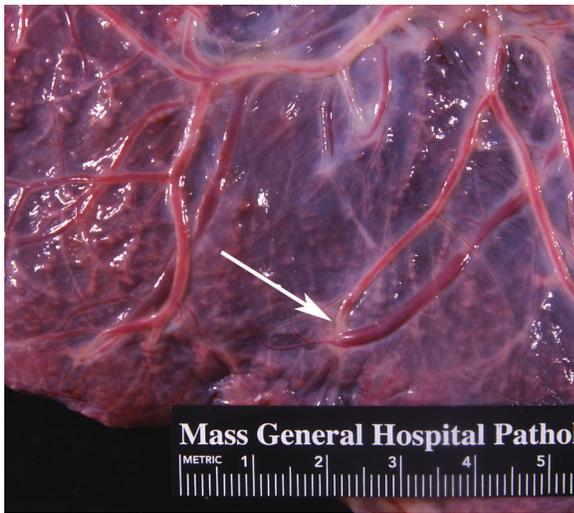Numerous cotyledons/lobules are seen grossly.

Figure 1-19

CHORIONIC PLATE

A paired chorionic plate artery and vein terminate to perfuse a lobule (arrow).

branches splitting off from the large mother branch. About two thirds of placentas show the dispersal pattern (37). The magistral/monopodial pattern has been associated with abnormal cord insertions and may be more efficient at delivering blood to distant lobules (38).

The placental membranes form from the expansion of the amniotic cavity and senescence of the trophoblast in this pole of the early circumferential placenta. The primitive placenta at the antiembryonic pole becomes attenuated, and the EVT cells at this location lose their ability to invade. Some placentas retain the capability of this trophoblast to invade and the chorion to form villi, as in the rare placental membranacea (see chapter 5-3). The presence of CT in the chorion laeve has been proposed as a cause (39). Normally, this inert region of the placenta will be "pushed" to the opposite side of the endometrial cavity, fusing with the decidua vera. The layers of the membranes then

Figure 1-20

CHORIONIC PLATE VESSELS

Placenta showing dispersal pattern of chorionic plate vessels from a central umbilical cord.
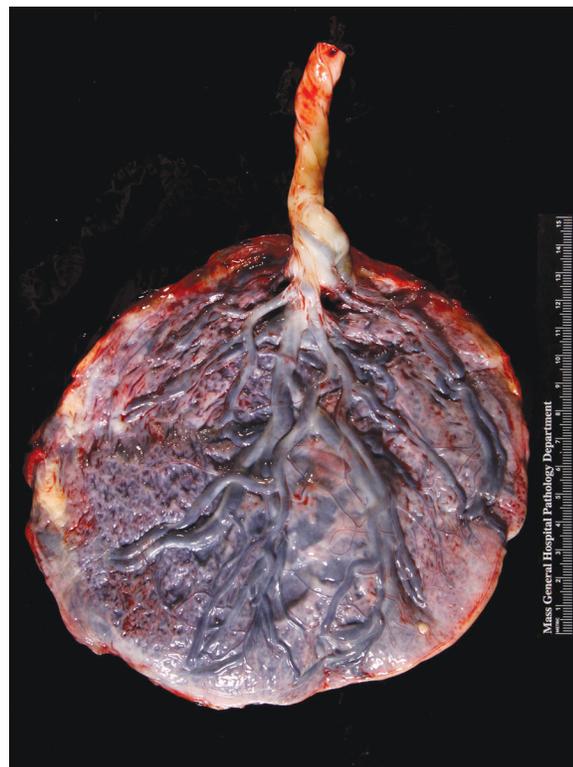

Figure 1-21

CHORIONIC PLATE VESSELS

Placenta showing magistrate pattern of chorionic plate vessels from a marginal insertion of the umbilical cord.
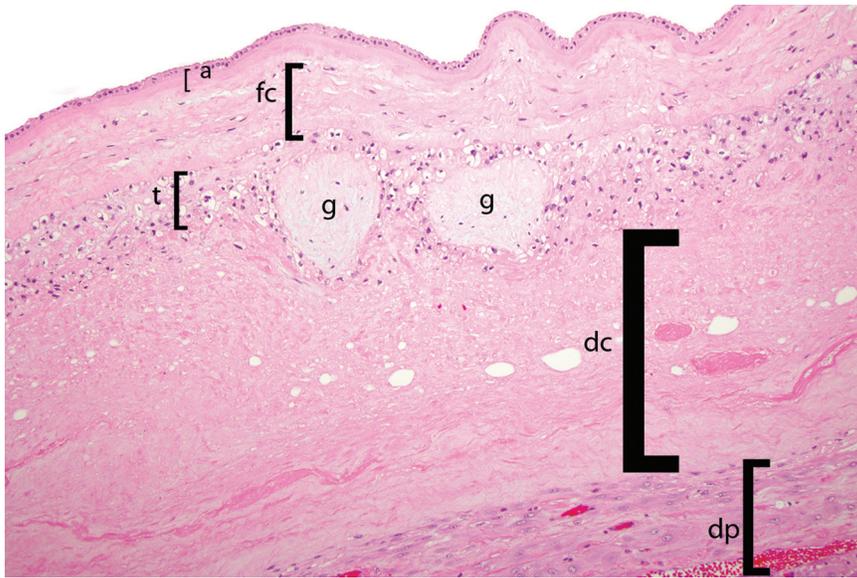
Figure 1-22

PLACENTAL MEMBRANES

Layers of the placental membranes are: amnion (a), fibrous chorion (fc), chorion laeve trophoblast (t), ghost villi (g), decidua capsularis (dc), and decidual parietalis/vera (dp).
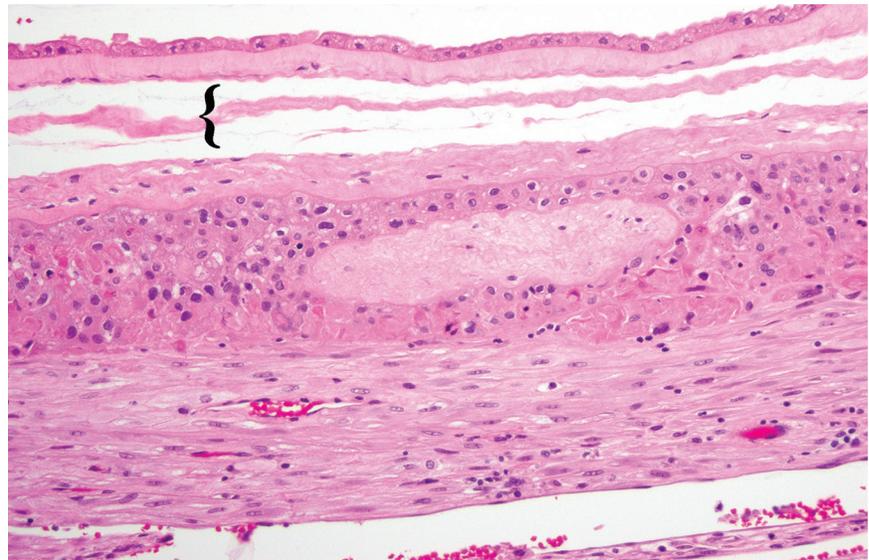

Figure 1-23

PLACENTAL MEMBRANES

The loose connection of the fibrous chorion to the amnion is seen highlighted by the {.

include (from the outside in): decidua vera (also termed decidua parietalis), decidua capsularis, primitive and necrotic primary villi, chorionic epithelium (the chorion laeve [smooth chorion], chorionic mesoderm [fibrous chorion]), amniotic mesoderm, basement membrane, and amniotic epithelium (fig. 1-22). The amnion doesn't "fuse" to the chorion until after 12 weeks gestational age, and then never completely. There is often a space between the amniotic mesoderm and chorionic mesoderm (fig. 1-23) that can separate, and amniotic fluid contents may be pushed in during labor. Vernix, lanugo,

loose meconium, blood, and inflammatory cells may be seen in this space.

The umbilical cord develops from the connecting stalk, and the vessels from the embryo connect through it to the placenta. Normally, the umbilical cord should insert centrally into the placenta (fig. 1-20). Abnormal cord insertions (peripheral, marginal, and velamentous) maybe due to early regional placental necrosis or to a true placental developmental abnormality (chapter 4-2). The umbilical arteries arise from the anterior division of the internal iliac artery. The umbilical vein returns

oxygenated blood from the placenta to the fetus through the ductus venosus to the inferior vena cava. The umbilical cord vessels are not innervated.

VASCULAR CIRCULATION OF THE PLACENTA

The fetal circulation of the placenta is a closed loop by which the fetus, via the umbilical arteries, chorionic plate vessels, villous arteries, and capillaries, perfuses the villi. Blood returns to the fetus via villous veins and the umbilical vein. The fetal perfusion of the placenta takes one fifth to one third of the fetal cardiac output (40). In a full-term fetus, the placenta contains about 33 percent of the total fetal blood volume. The capillary network is rich in the terminal villi where the exchange of gases and nutrients from the maternal circulation occurs via diffusion across the vasculosyncytial membranes or from the transport function of the ST.

Maternal circulation to the placenta is via around 120 spiral arteries perfusing the placental lobules at a rate of approximately 600 mL/minute at a low pressure of 70 mmHg in the spiral arteries, which falls to 10 mmHg in the intervillous space (41). The placental circulation takes approximately 12 percent of the maternal cardiac output at term (42). Maternal arterial perfusion is focused centrally in the disc. The maternal vascular space in the placenta is similar to an arteriovenous malformation in which the arterial and venous blood are admixed in the relatively vast maternal space (43).

The maternal venous return is through endometrial/myometrial venous channels, which are positioned parallel to the basal plate and are enhanced in the periphery of the placenta. This marginal sinus is another weak link in the placenta and is prone to hemorrhage, resulting in premature separation of the placenta (marginal placental abruption). Changes in pressure and flow rate can drastically alter the normal perfusion of the villi and are thus carefully controlled via the vascular remodeling that takes place in early placental development.

FUNCTIONS OF THE SYNCYTIOTROPHOBLAST

The ST is critical for many of the functions of the placenta to ensure fetal growth and well being. The ST is a metabolically active epithe-lium in which the transport of nutrients and waste products takes place via active transport, diffusion, facilitated transport, and endocytosis/exocytosis (44–46). The placenta also metabolizes some products prior to transport to the fetal side, such as lipids and some amino acids (47). Transport molecules must shuttle nutrients to the fetus from the maternal vascular side of the ST, from its microvillous membrane to the basement membrane side (fetal) side of the ST. Transport from the fetal side to the maternal side also removes waste products. The ST transport function is adaptable based on fetal demand and maternal supply (45,46,48), and has implications for pathologies of fetal growth.

ST also acts as an endocrine organ with synthesis functions for hormones and other bioactive factors necessary for placental development, growth and maintenance of the pregnancy. An important function of the ST is to provide a barrier separating the maternal and fetal components of the placenta. This barrier function of the ST helps protect the early conceptus from infection. The ST layer acts as an endothelium of sorts on the villi to the maternal blood. The ST is exposed to the maternal blood throughout pregnancy once perfusion has begun at around 10 to 12 weeks' gestational age. ST evades maternal immunodestruction in part by being HLA-A,B null (49).

The ST is generated by fusion of the differentiating CT to the existing villous ST and occurs throughout gestation. Therefore, the ST nuclei are of variable ages. There is a normal shedding of senescent ST nuclei into the maternal vascular space. These shed ST cells first form knots of pyknotic cells that protrude from the villi (fig. 1-15), are a feature of mature placentas, increase with senescence and hypoxia, and are often present and increased as a feature of maternal vascular malperfusion (see chapter 8-3).

Breaches in trophoblast barrier function from apoptosis, necrosis, shear stress, or infection result in exposure of the villous stroma to maternal blood, resulting in fibrin deposition on the villi (fig. 1-24). We believe this is the etiology behind villous fibrinoid necrosis in which fibrin can totally replace the villous stroma (fig. 1-25) (50). These lesions are commonly present in placentas and may be evidence of trophoblast damage (50). Approximately 7 percent of the villous surfaces in normal term human placentas show
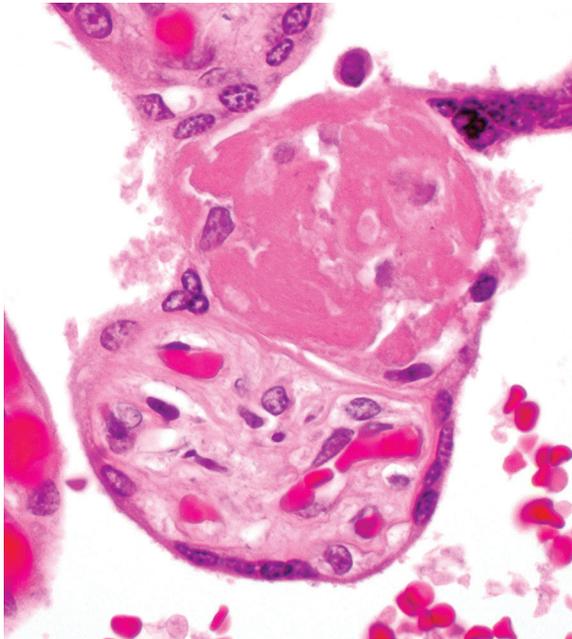
Figure 1-24

FOCAL TROPHOBLAST FIBRINOID NECROSIS

A fibrinoid nodule is present on the surface of a trophoblastically denuded villus.
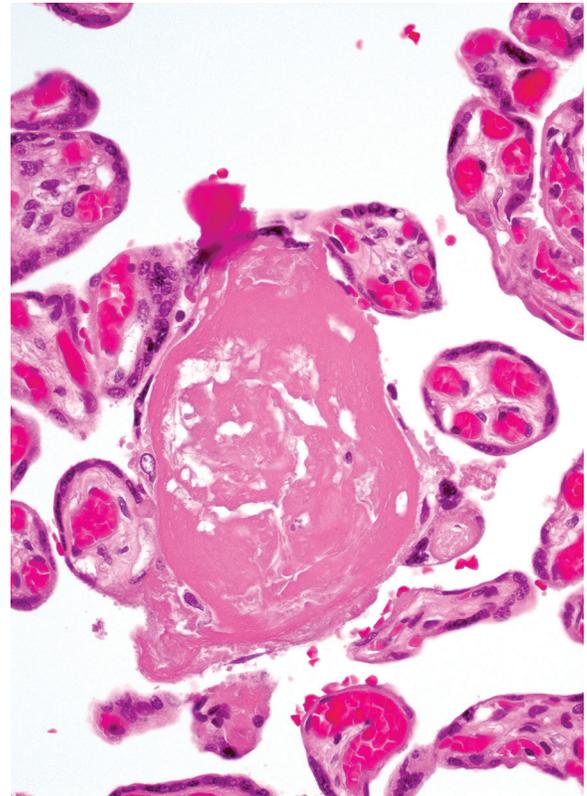

Figure 1-25

TROPHOBLAST FIBRINOID NECROSIS

Fibrinoid material and surface re-epithelialization by syncytiotrophoblast.

foci of villous fibrinoid necrosis (51). Increased villous fibrinoid necrosis has been described in diabetic pregnancies (52,53) and in pregnancies complicated by hypertension (50).

HISTOLOGIC ANATOMY

The placental disc, when viewed on cross section, is composed of the chorionic plate, the parenchyma, and the basal plate (fig. 1-26). The chorionic plate is composed of amnion, connective tissue in which the chorionic vessels reside, and chorion frondosum (fig. 1-27). The chorion frondosum is a trophoblastic layer from which the stem villi emerge early in placentogenesis. Despite this, there is often scant trophoblast present in the chorion frondosum, especially in the later half of pregnancy. Early in gestation, trophoblast can be identified in this region (fig. 1-28). The chorionic plate often has a thin layer of fibrin under the chorion frondosum, which may be due to turbulence and slow flow from maternal perfusion. This is a normal finding, and only when thick and grossly nodular, is it interpreted as pathologic (increased subchorionic fibrin) (fig. 1-29).
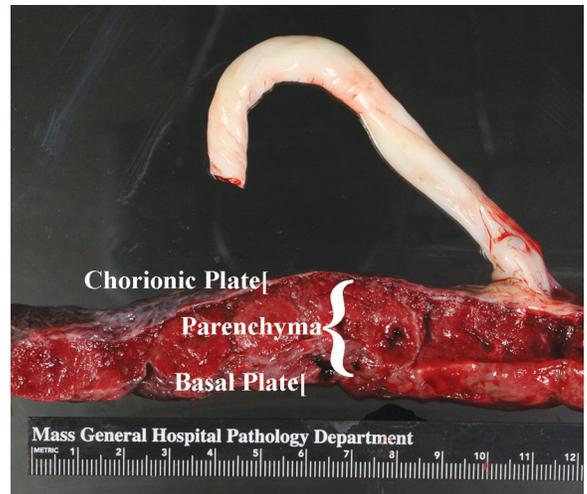

Figure 1-26

TERM PLACENTA

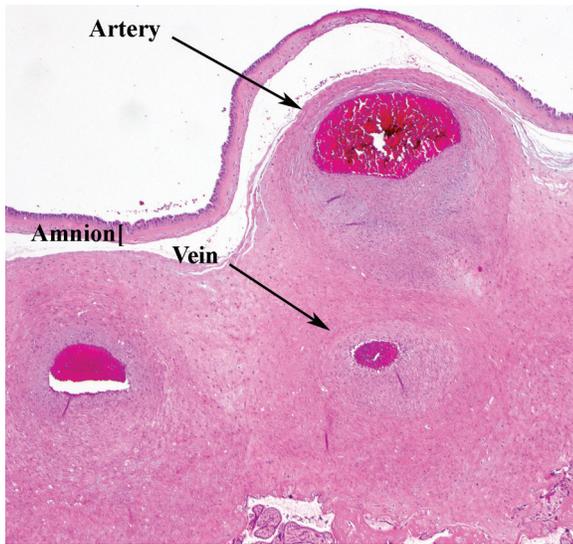Slab section of a term placenta showing the geography.

Figure 1-27

CHORIONIC PLATE

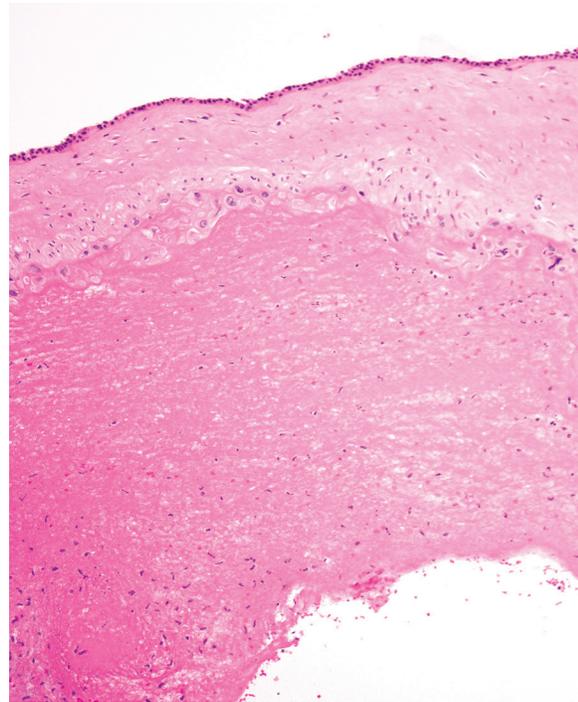It is possible to discern artery from vein due to the position of the artery on top of the vein.
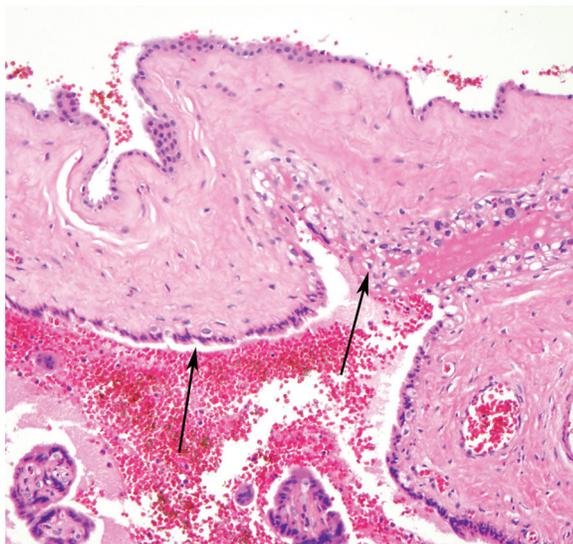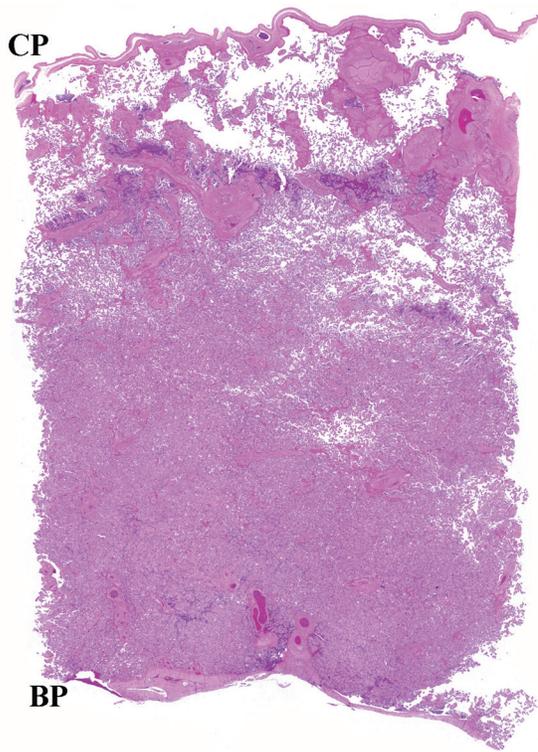

Figure 1-28

CHORIONIC PLATE

In a second trimester placenta, chorionic plate with presence of chorionic epithelium in the subchorionic layer (arrows).

The subchorionic space is an early site of acute chorioamnionitis (see chapter 5-5). Due to the chorionic plate's proximity to the amniotic cavity, chemoattractant signals can result in margination

Figure 1-29

SUBCHORIONIC FIBRIN

The subchorionic fibrin is increased.

of circulating maternal inflammatory cells into the normally acellular subchorionic fibrin. This is an early stage of the maternal inflammatory response. Other pathologies of the chorionic plate are described in chapter 6.

The parenchyma is composed of the villi: stem, intermediate, and terminal villi (depending on gestational age). The villi closest to the chorionic plate are less well perfused and thus more hypoxic than those in the central area or at the basal plate (fig. 1-30). These villi in the upper third of the parenchyma are sparser and show features generally associated with ischemia (increased intervillous space, smaller villi, more and larger syncytial knots), often with increased intervillous fibrin deposition. The villi in the center third and deeper third of the placenta on cross section are better perfused and oxygenated, and should not be ischemic. They should show a good packing density, good distribution of villous types with a predominance of terminal villi by third trimester, and no or little intervillous fibrin. The deepest villi, those
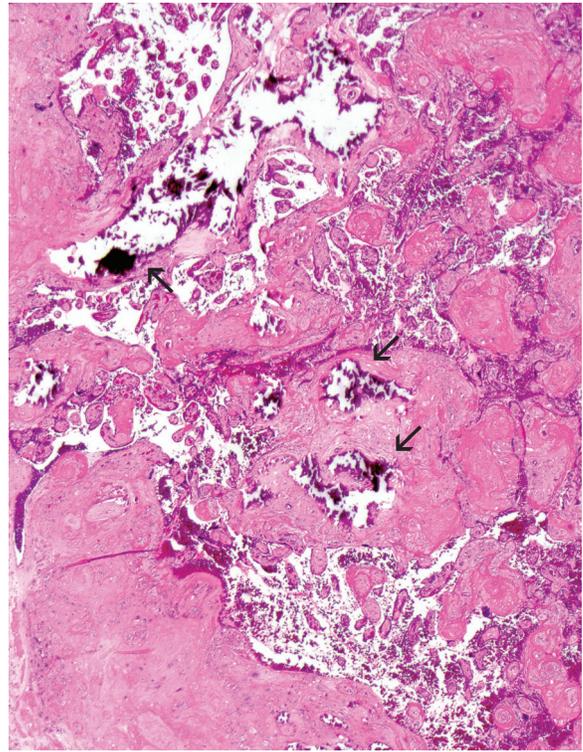
Figure 1-30

TERM PLACENTA

Full-thickness photomicrograph of a term placenta. There is an increase in intervillous space in the upper one third of the placenta under the chorionic place (CP) and much denser villi in the lower two thirds of the parenchyma. (BP = basal plate.)

Figure 1-31

PARENCHYMA

There is increased dystrophic villous and extravillous calcification (arrows).

closest to the basal plate, are the best oxygenated and are often more immature in appearance. To determine maturation of the placenta, the villi in the middle third of the parenchyma are assessed, avoiding overcalling accelerated maturation or distal villous hyperplasia by examining the villi closest to the chorionic plate or worrying about delayed villous maturation when examining the most basal villi.

A common finding in the parenchyma is scattered coarse calcifications. These can be identified grossly as coarse punctate yellow-white lesions typically along the basal plate. They are present in the villi or intervillous fibrin, more common at term or post-dates, and are a feature of placental senescence (fig. 1-31). If present preterm, one must be concerned about MVM. Some term or post-term placentas are so calcified that the delivering clinician notes it. Usually, calcifications

are ignored unless noted by the clinician, are present preterm, or are markedly excessive (you will know it when you see it!). A diagnosis of "increased dystrophic calcifications" is appropriate and try to decipher if it is a pathologic finding or not by the company they keep (e.g., associated with infarcts, increased perivillous fibrin, or other features of maternal vascular malperfusion) (see chapter 8-3).

The intervillous space (maternal space or maternal lakes) contains circulating maternal blood, which should be predominantly red blood cells. In most placentas from labored deliveries there is scant maternal blood in the maternal space after delivery, but congestion can be seen, especially in unlabored cesarean deliveries. In the first trimester, there is limited maternal perfusion to the placenta, therefore the intervillous space should be empty. Any fibrin or maternal blood in that space suggests pathologic implantation and failure of the eEVT to plug the maternal vessels. This results
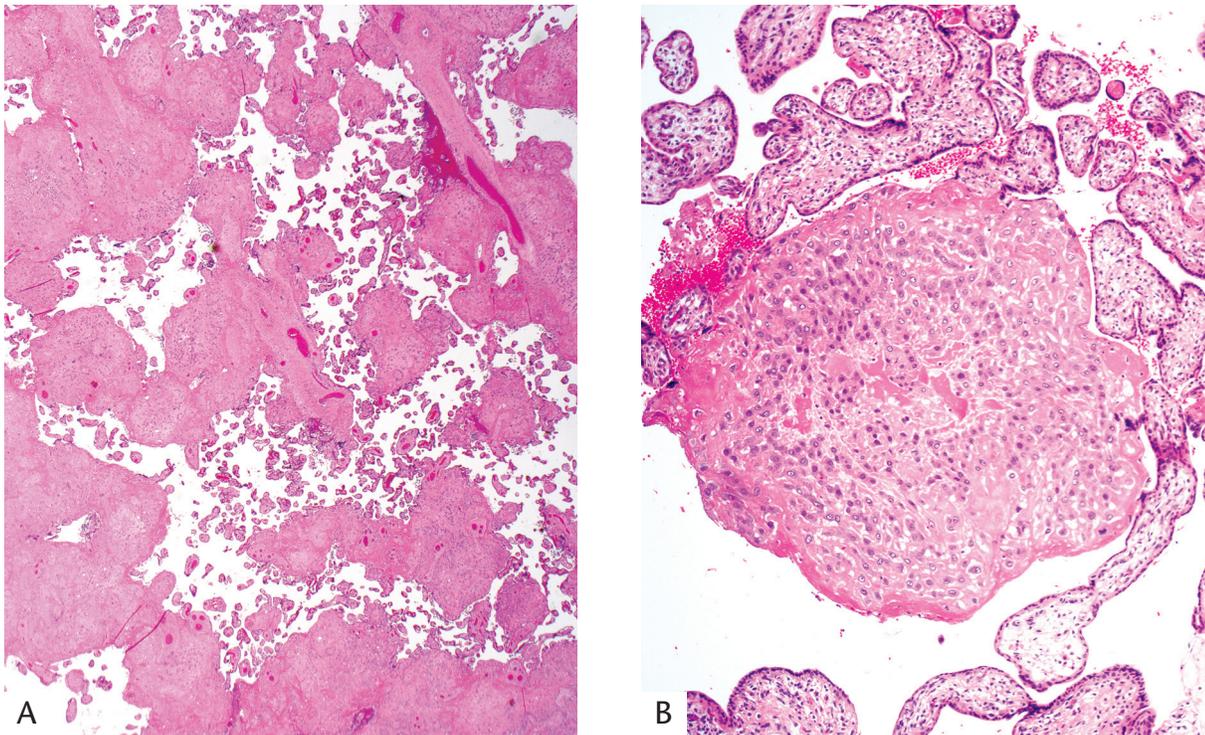
Figure 1-32

TROPHOBLASTIC FIBRINOID ISLANDS

A: Low-power view of many trophoblast islands in this subchorionic region of a term placenta.
B: Higher-power view shows an irregular-shaped nodule of fibrin/fibrinoid with trophoblast.

in blood and fibrin in the maternal space and is concerning for pathologies of implantation and the diagnosis of massive perivillous fibrin deposition (see chapter 8-7). Cells in the intervillous space should be examined as they represent those present in the circulating maternal blood. Sickled red blood cells, histiocytes, and hematogenously spread malignancies can be identified in the maternal space. The most common finding in the intervillous space other than blood is fibrin, which can be a benign feature at the margins of the placenta or toward the chorionic plate in the third trimester, but is always pathologic in the first and second trimesters (see chapter 8-7).

Other normal findings in the intervillous space include trophoblastic fibrinoid islands, septa, and septal cysts. Trophoblastic fibrinoid islands are nodules of fibrin/fibrinoid and trophoblast, which tend to be present toward the chorionic plate (fig. 1-32). When extensive and deep, they may be associated with mater-

nal vascular malperfusion. Placental septa are folds of the basal plate consisting of fibrin/fibrinoid, decidua, and trophoblast, and are benign features of normal placentation that trace the borders of the placental lobules (fig. 1-33). They can undergo cystification that will be filled with amorphous clear to eosinophilic material (fig. 1-34). Septal cysts are a feature of mature placentas, rare in preterm placentas (54). They occur with edematous placentas and are increased in placentas of diabetics. They are also increased in hypertensive disorders and immune hydrops, and occur earlier in gestation with these complications of pregnancy. These cysts can thrombose and appear grossly and histologically similar to an intervillous thrombus.

The basal plate includes the basal most villi, Rohr's and Nitabuch's fibrin, decidua basalis, EVT, spiral arterioles, venules, and occasional endometrial glands (fig. 1-35). The basal plate should have only transformed arterioles from the implantation process; nontransformed or
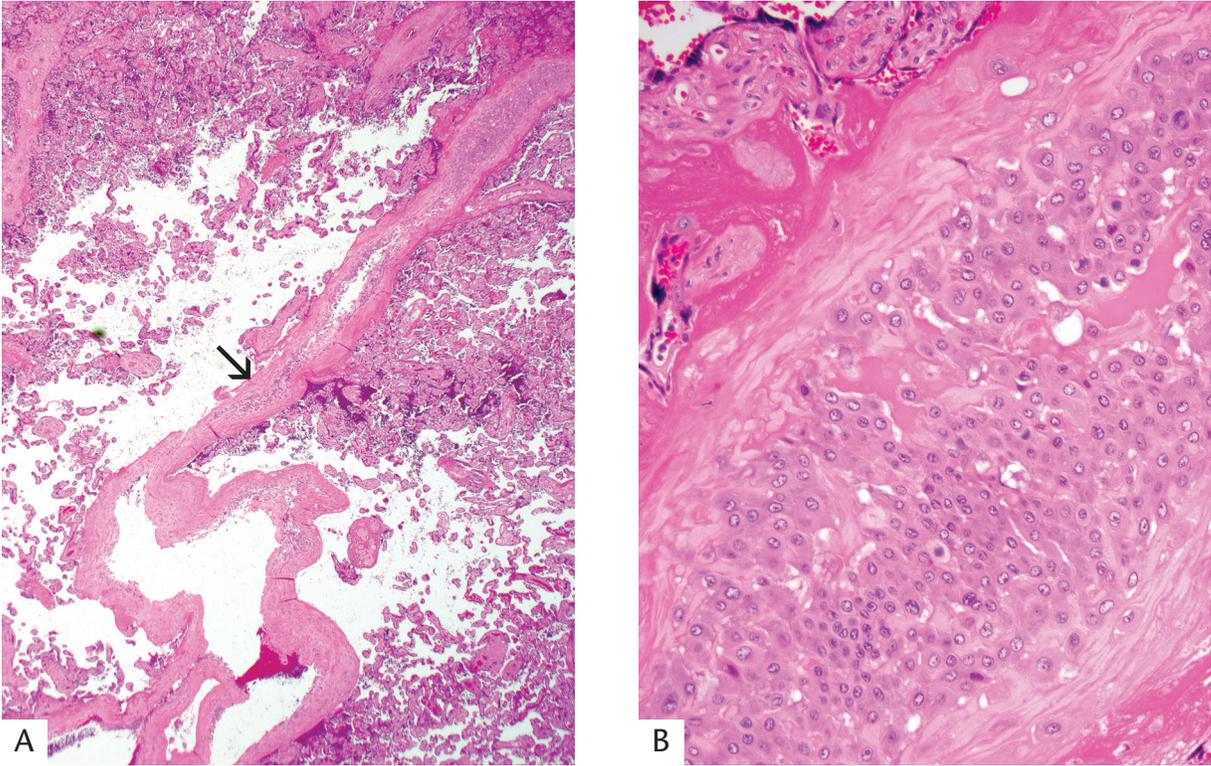
Figure 1-33

INTERVILLOUS SEPTA

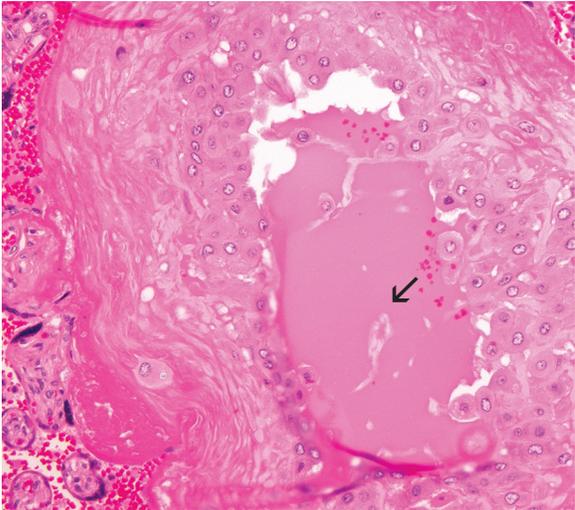Low power (A) (arrow) and higher power (B).

Figure 1-34

SMALL SEPTAL CYST
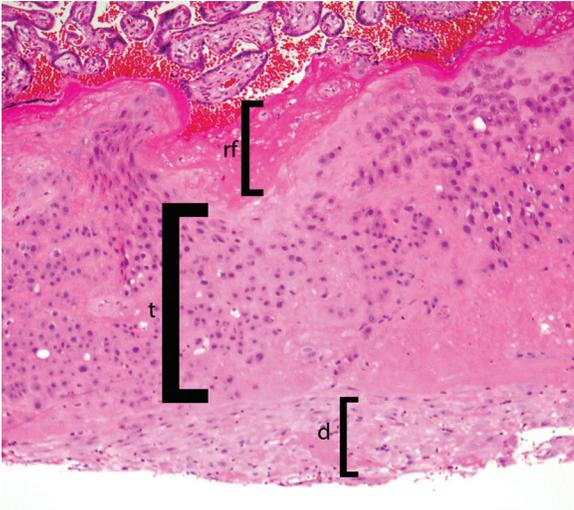
The cyst is filled with eosinophilic fluid (arrow).

Figure 1-35

LAYERS OF THE BASAL PLATE

rf = Rohr fibrin, t = trophoblast in Nitabuch fibrin, d = decidua basalis.

Figure 1-36

UMBILICAL CORD

There are two arteries, one vein, Wharton's jelly, and surrounding amnion.
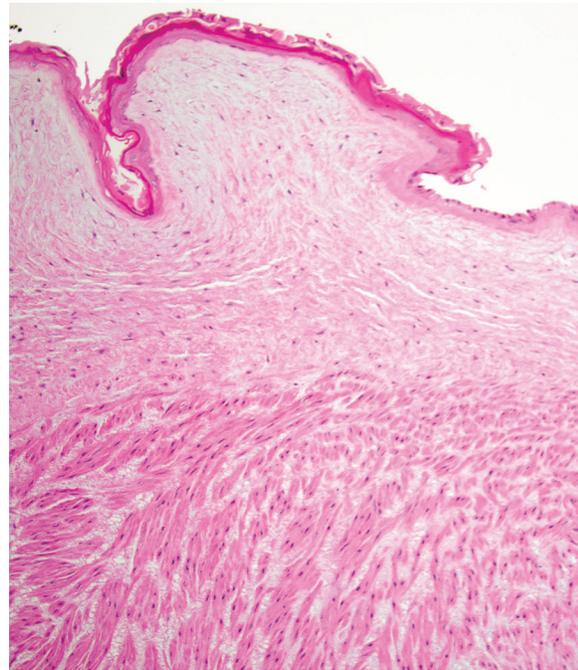

Figure 1-37

**SQUAMOUS METAPLASIA OF
THE UMBILICAL CORD AMNION**

This is a common finding of no clinical significance.

incompletely transformed arterioles are pathologic and part of the spectrum of decidual arteriopathy (see chapter 5-10).

There is often a mild mixed acute and chronic inflammatory process in the decidua basalis but this should not be excessive or contain plasma cells. If so, then chronic deciduitis should be ruled out (see chapter 7-3). The basal plate is an important region for pathologic processes, especially those related to abnormal implantation and maternal vascular malperfusion, immunologic phenomena, for example, the interface pattern of villitis of unknown etiology or plasma cell/chronic deciduitis, abnormal fibrin deposition as in maternal floor infarction, and evidence of morbidly adherent placenta with basal plate myometrial fibers. A careful evaluation of the maternal floor/basal plate for vascular and inflammatory pathologies, and the presence of adherent myometrial fibers, should be a routine part of the placental examination.

The umbilical cord is composed of three non-innervated vessels: two arteries and a single vein within a specialized myxoid stroma called Wharton's jelly as well as a few resident inflammatory cells (rare histiocytes and basophils) surfaced by amnion (fig. 1-36). This amnion is often metaplastic (as is the amnion on the

membranes and chorionic plate), commonly demonstrating squamous metaplasia (fig. 1-37). Occasionally, remnants of embryologic structures are seen in the umbilical cord (e.g., the vitelline duct or allantoic duct). Many clinically important pathologies can be diagnosed by careful examination of the umbilical cord or can be implicated by "downstream" pathologies (e.g., fetal vascular malperfusion).

The placental membranes are composed of the amnion, chorion laeve, and decidua (fig. 1-22, described above). The amnion is typically a low cuboidal epithelium (fig. 1-38A) but often shows benign squamous metaplasia (fig. 1-38B). Amniocytes contain central nuclei and scant eosinophilic to clear cytoplasm (fig. 1-38A). With exposure to meconium, blood, or acute inflammatory cells in the amniotic cavity, or in cases of marked oligohydramnios, the amniocytes can become reactive and show columnar, papillary, or transitional metaplasia (fig. 1-38C). We call this "angry" amnion! With prolonged exposure, amniotic cell drop out or frank necrosis occurs.
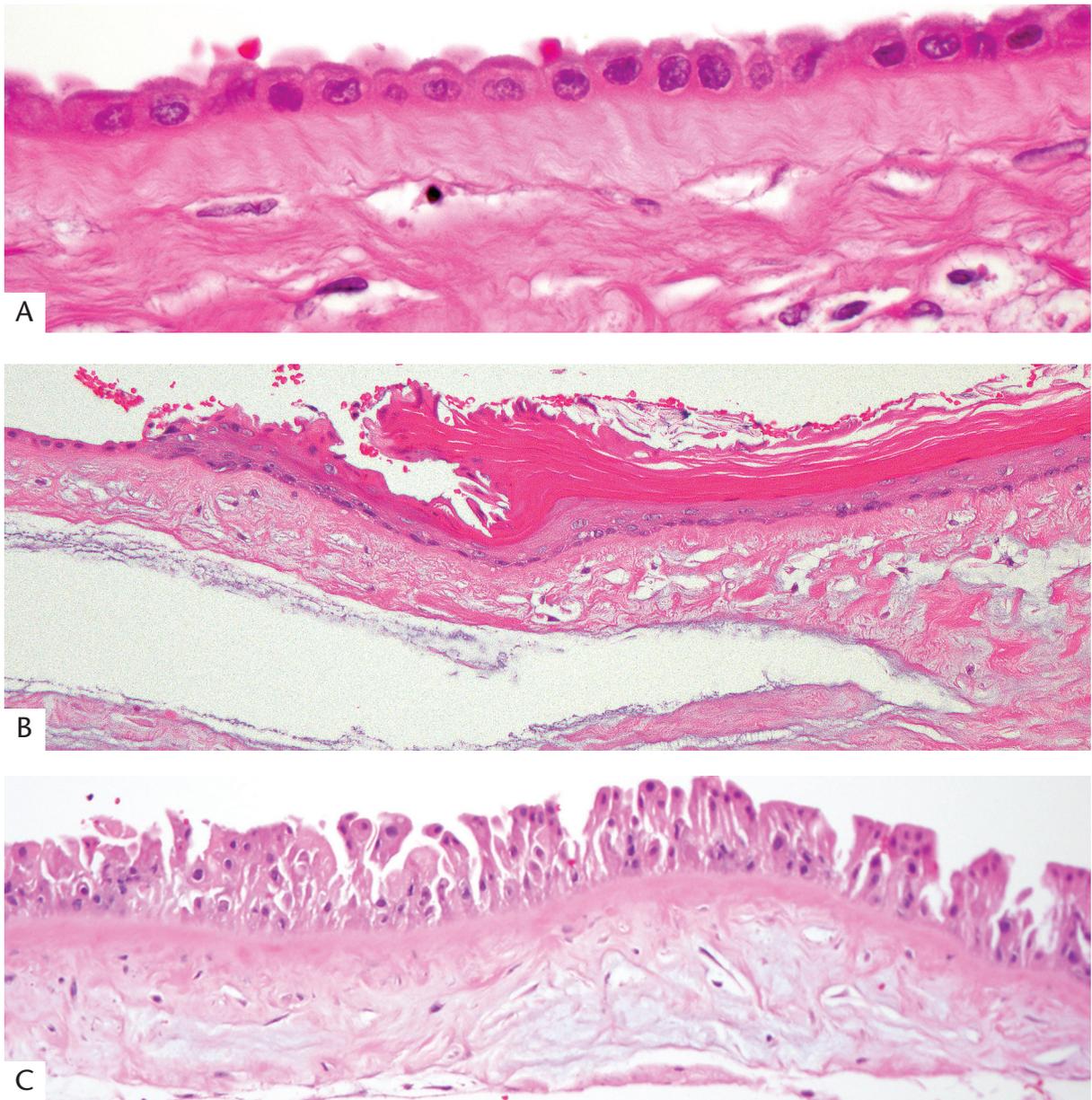
Figure 1-38

PHENOTYPES OF MEMBRANOUS AMNION

A: Low cuboidal with granular eosinophilic cytoplasm.

B: Squamous metaplasia, a common finding of no clinical significance.

C: Papillary metaplasia of the amnion, a common feature of amniotic irritation from meconium, chorioamnionitis, or oligohydramnios.

Deep to the amniotic epithelium is a basement membrane followed by a band of acellular collagen. The fibrous chorion "adheres" loosely to this collagen and is composed of loose, sparsely cellular, fibrous tissue resting on the tropho-blastic layer of the chorion laeve. The amnion can become separated from the chorion due to this loose adherence. This occurs with handling, especially when there is meconium exposure or acute chorioamnionitis. Even without separation
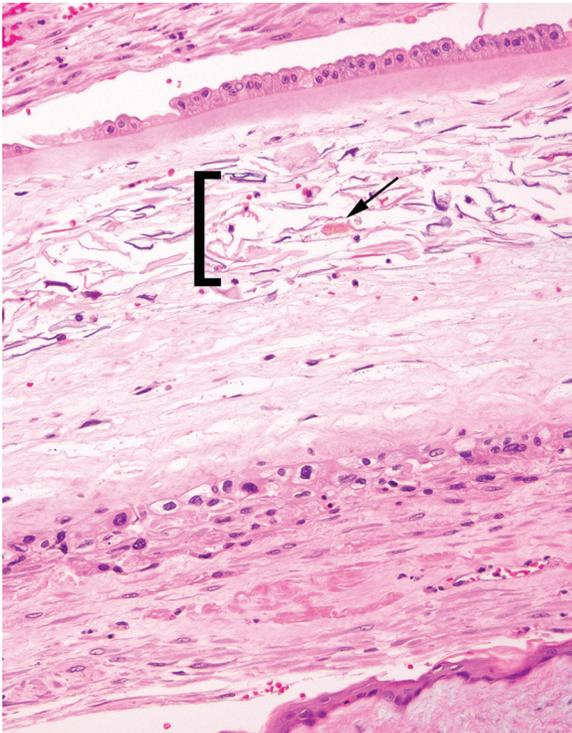
Figure 1-39

VERNIX CASEOSA

Vernix caseosa and loose meconium (arrow) in the space between the chorion and amnion in the free membranes.

of the amnion and chorion, debris is often seen in that space with the rupture of membranes and labor. A common finding is the presence of vernix caseosa in this space (fig. 1-39).

The epithelial chorion laeve (smooth chorion) is composed of medium to large polyhedral epithelial trophoblast cells that are mononuclear or binucleated. The nuclei are round or irregular/angular in shape, with smudgy senescent-appearing chromatin and occasional nucleoli. The cytoplasm is often clear but can be pale or densely eosinophilic (fig. 1-40). These cells stain for keratins (AE1/3, CK7), and are HLA-G positive. Unlike the trophoblast cells in the decidua basalis, those in the chorion laeve are p63 positive. Often, in the smooth chorion laeve, or just beneath it, there are the ghosts of the original secondary villi formed early during placentogenesis when the placenta is spherical. Some placentas have a lot of these ghosts; in others they are sparse (fig. 1-41). They are normal structures that should not be confused with other potentially pathologic findings including chorionic pseudocysts or granulomas.

The decidua deep to the chorionic epithelium is composed of at least two layers: decidual capsularis (which is often very thin and necrotic)
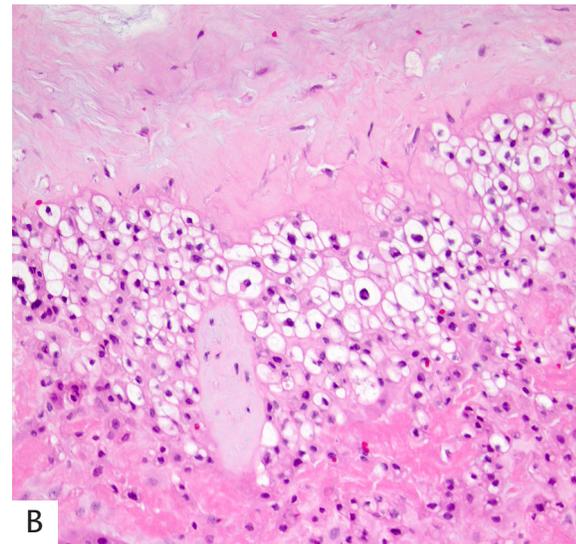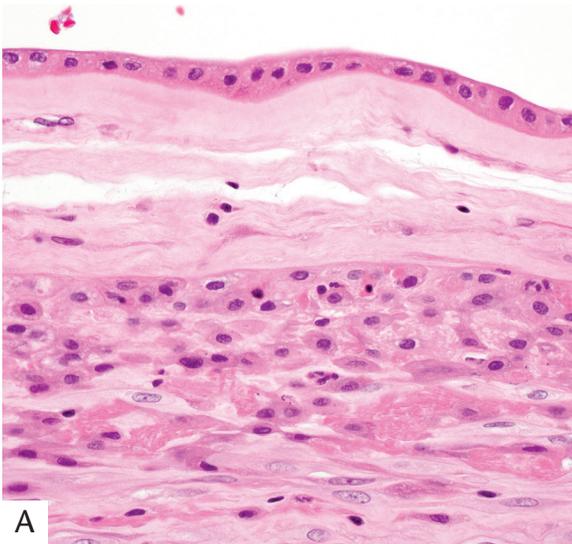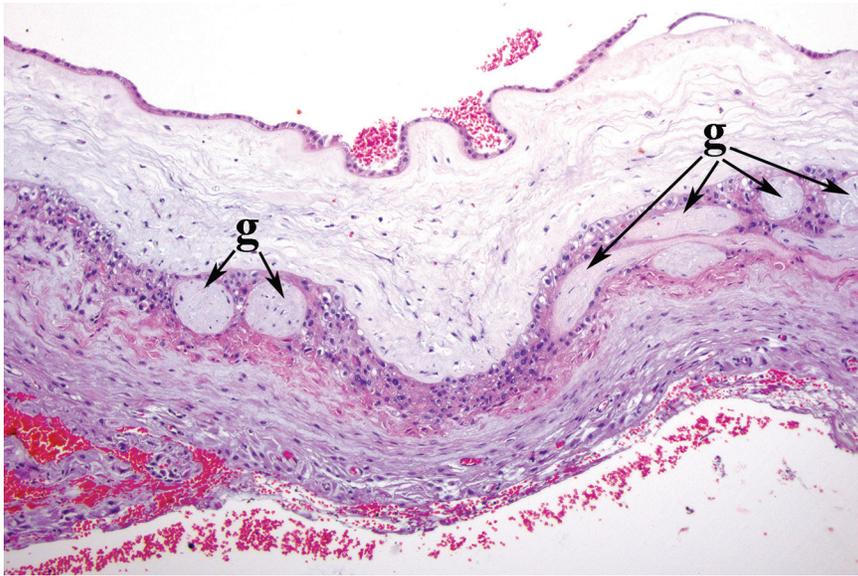

Figure 1-40

PHENOTYPE OF THE TROPHOBLAST IN THE CHORION LAEVE

A: Eosinophilic cytoplasm and small central nuclei.
B: Clear cytoplasm and larger more pyknotic nuclei.

Figure 1-41

GHOST VILLI

Membranes showing many ghost villi (g).

and decidua parietalis (also known as the decidua vera). These contain the terminal arterioles of the spiral arteries, and can contain venules and endometrial glands. These vessels in the decidua parietalis have not been remodeled and have not been invaded by EVT since the trophoblast in the chorion laeve is inert and does not retain invasive properties. Therefore, these vessels should be small, contain no fibrinoid necrosis or mural hypertrophy, and are a marker of the state of the vessels, at least locally in the uterus, if not systemically.

The pathology of these vessels is discussed in chapter 5-10. There is usually a mixed acute and chronic inflammatory infiltrate in the decidua of the membranes, especially if there has been labor. The inflammatory cells must reach into the chorion to consider a diagnosis of acute or

chronic chorioamnionitis, or be extensive or contain plasma cells for a diagnosis of chronic deciduitis. Another common finding in the decidua of the membranes is hemorrhage, either remote or fresh. Hemosiderin-laden macrophages in the decidual parietalis are common and suggests antenatal bleeding. A given membrane roll may not contain decidua parietalis due to cleaving at this junction for delivery, and this unfortunately negates diagnosis of the many pathologies.

In summary, the placenta is a complex organ developed from the specialized trophoblastic epithelium. The discoid hemochorial human placenta is a markedly vascular and metabolically active organ perfused from two individuals and maintained in an immunologically privileged environment. Pathologies from three sources are possible: maternal, fetal, and the placenta itself.

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