20
Infectious Diseases

Prenatal infections are important aspects of placental pathology. They are common and varied. Their pathogenesis and related circumstances must be understood if the pathologic lesions are to be interpreted correctly. Many types of infection cause placental changes, but in some types the infection may be difficult to prove from placental examination. Ultrastructural studies are especially lacking in this area and might be helpful, particularly when virus infection is suspected. Infections may ascend from the endocervical canal, or they may reach the placenta hematogenously through the maternal blood. Rarely are they acquired by amniocentesis, chorionic villus sampling, amnioscopy (Horky & Amon, 1967), percutaneous umbilical blood sampling (PUBS; Wilkins et al., 1989), or intrauterine fetal transfusion (Goodlin, 1965; Scott & Henderson, 1972). Many infections cause gross and microscopic changes of the placenta, but others, for example, the Coxsackie virus infection, leave few characteristic or specifically recognizable traces. This is also the case with parvovirus B19 infection, which often leads to fetal hydrops but has no specific placental alteration other than perhaps intranuclear inclusions in nucleated red blood cell precursors and endothelium, as a report by Hartwick et al. (1989) showed. Samra et al. (1989) described villous necrosis and calcification in the placenta from a 20 weeks' gestation with hydrops due to this infection (see Chapter 16).

This chapter first covers chorioamnionitis, followed by infections with specific organisms that correlate with chorioamnionitis. Syphilis and necrotizing funisitis (inflammation of the umbilical cord) are next discussed, and then the virus infections and villitides are discussed. Finally, rare infectious diseases such as malaria and parasitic infections are covered. A complete review of the early literature, especially the European references, may be found in the work of Flamm (1959). The comprehensive text on infections of the fetus and newborn infant by Remington and Klein (1983) can also be consulted. Excellent and complete reviews of fetal and placental infections have been provided by Blanc (1981), Altshuler (1984, 1996), Carroll et al. (1996), and Wigglesworth (1996). Most recently, Hirsch and Wang (2005) have produced a mouse model for the study of banal infections and comprehensively reviewed the literature. They propose that the process begins with toll-like receptors (TRLs) and, once the cascade is established it is difficult to interrupt.

Chorioamnionitis

Macroscopic Appearance

Typically, the placenta of the amnionic sac infection syndrome is premature. It lacks the blue sheen of the normal immature organ, and the membranes are obscured by an inflammatory exudate of polymorphonuclear leukocytes (PMNLs, neutrophils) (Figs. 20.1 to 20.3). The surface becomes yellow when much leukocytic exudate has accumulated and when the process has been of long duration. The amnion may be roughened or have lost the luster it normally possesses. The placenta is also frequently malodorous, and the astute observer may identify the prevailing organism by the odor. Thus, the fecal odor of fusobacterial and *Bacteroides* infections, and the sweet odor of *Clostridium* and *Listeria* infections are useful identifiers. The membranes are typically more friable, and the decidua capsularis is frequently detached and hemorrhagic and may even be absent in the placental specimen having been left in the uterus to be later discharged as lochia. These prematurely delivered placentas are often accompanied by an acute marginal hemorrhage that undermines the edge of the placenta and that originates from deciduitis. Harris (1988) has described this in greater detail. Although this mimics abruptio placentae, this hemorrhagic process (Figs. 20.4 and 20.5) markedly differs from the typical abruptio placentae of preeclampsia, the *retroplacental* hematoma. Vintzileos et al. (1987) believed that true abruptio occurs after premature rupture of the membranes. They found an incidence of 6.3% (control 2.7%) of normally implanted placentas with "indentations in the placental substance." Unfortunately, they did not discuss inflammatory reactions. Gonen et al. (1989) also provided evidence that abruptio (loosely defined) is frequently preceded by prolonged rupture of membranes. Darby et al. (1989) compared severe preterm abruptions with control women requiring preterm delivery. The former group had significantly more frequently chorio-

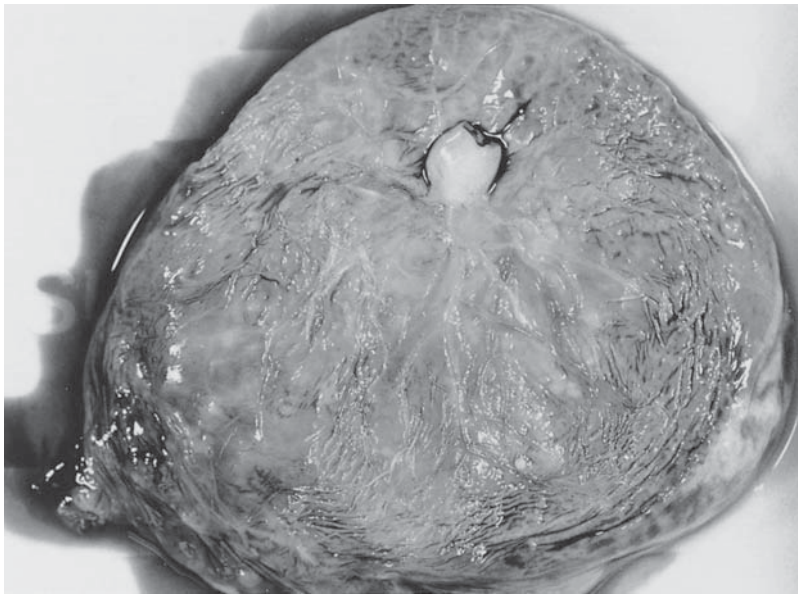

FIGURE 20.1. Near-term placenta with severe chorioamnionitis. Note the marginal hemorrhage at left, caused by deciduitis. The surface of the placenta is obscured by a whitish exudate that obscures the normal underlying blue color; the vasculature is also indistinct. Neonatal death.

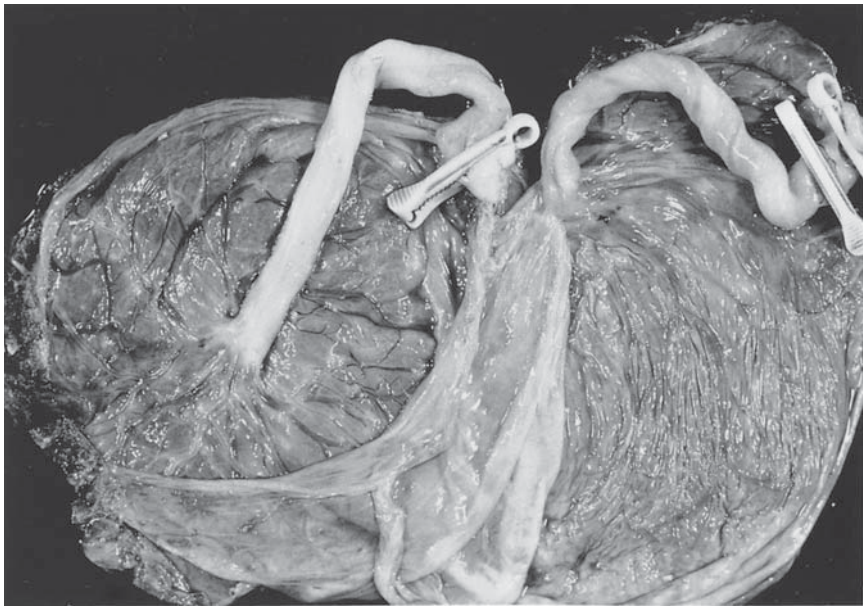

FIGURE 20.2. Immature diamnionic, dichorionic twin placenta from a cesarean section. Twin A (left, one cord clamp) was located higher in the uterus; twin B (right), with a marginally inserted cord, was near the lower uterine segment and had significant chorioamnionitis. Compare the luster of the normal placenta (left) with the indistinct features of the abnormal placenta (right), which are due to inflammation. Neonatal deaths.

FIGURE 20.3. Immature twin placenta (19 weeks' gestation) from which twin A (right) had been delivered 1 week prior to twin B (left). Both twins had severe chorioamnionitis and fatal aspiration pneumonia. The placental surface was yellow, purulent, and malodorous.

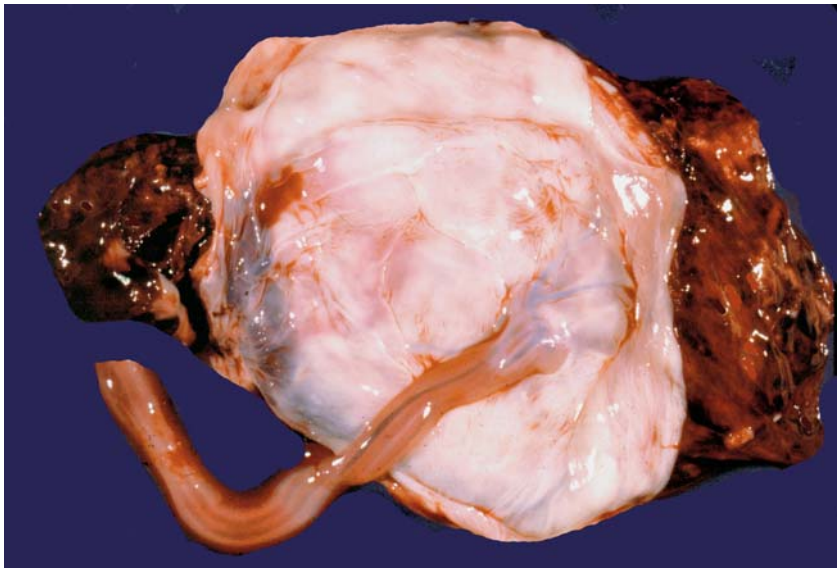

FIGURE 20.4. Placenta at 21 weeks' gestation with massive chorioamnionitis and marked marginal/retroplacental hemorrhage caused by deciduitis.

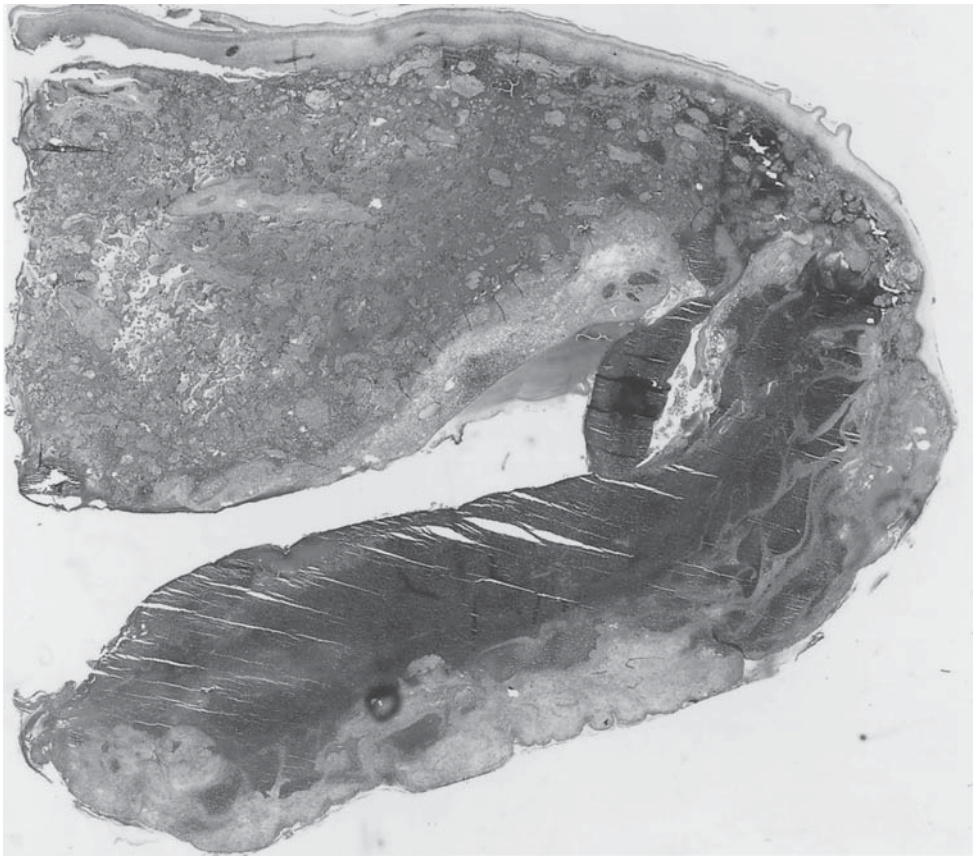

FIGURE 20.5. Margin of immature placenta at 23' weeks gestation with marked chorioamnionitis and abruptio. The abruption is represented by the dark marginal retromembranous hematoma which originates from marked deciduitis and its disrupted vessels. (H&E ×3.5).

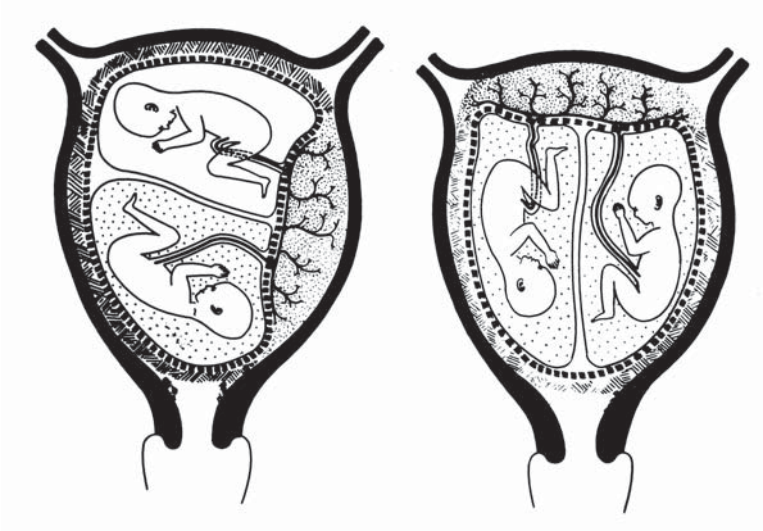

FIGURE 20.6. Twin placentation with inflammation (stippled), explaining the ascending nature of the infection.

amnionitis and funisitis (41% versus 4%). They also believed that infection preceded abruptio, whereas Major et al. (1995) showed that rupture of membranes is often preceded by vaginal bleeding. This supports our notion that this decidual bleeding is secondary to deciduitis, and not the true abruptio placentae in the sense used in preeclampsia.

Touch preparations made from the fetal surface of placentas from women with prenatal infection may be used to identify the inflammatory exudate and the bacteria quickly, especially when the infection is due to *Listeria monocytogenes*. When chorioamnionitis is found in twin placentas, it is nearly invariably twin A whose cavity has inflammation or who has the more severely inflamed portion (Benirschke, 1960) (Fig. 20.6). We have considered this to mean that the amnionic sac infection is always ascending through the cervical canal. This correlation was questioned by Thiery et al. (1970), however, who found umbilical phlebitis in twin B as often as in twin A. These authors did not state how their twins were delivered, though, or how the twins were positively identified as to their intrauterine location. These specifications are crucial to the interpretation of such data.

Microscopic Appearance

Perhaps the earliest investigators to delineate chorioamnionitis were Wohlwill and Bock (1929), who described nine cases of "coccal" infection, some of which clearly followed attempted ("criminal") abortion. The reviews of Kückens (1938) and Müller (1956) made it clear that "round cell infiltration of the placenta" had been known before then. These authors suggested that infection of the fetus caused sepsis and then led to the placental inflammation. Wohlwill and Bock (1929) reviewed the placental inflammations that had been reported before their studies of chorioamnionitis (largely syphilis, tuberculosis, and leprosy) and decided that the coccal infection they found was of a different character.

An extensive description of chorioamnionitis ("round cell infiltration") was authored by Kückens (1938). He found the literature to be contradictory and came to the following conclusions: The decidua has some round cell infiltration in 60% to 70% of normal placentas; villi never have such cellular infiltrates or abscesses; chorioamnionitis, with leukocytic origin from the intervillous space, and funisitis are common perinatal phenomena. Kückens suggested that an ascending origin of the infection was the most likely pathway, and this was supported by Knox and Hoerner (1950) as well. Kückens found that, with funisitis, the umbilical vein is the first vessel to be involved, with arterial inflammation to follow. He identified cocci in the lesions, found an incidence of 20.4% chorioamnionitis, and related it to the length of labor and rupture of membranes. Interestingly, a correlation with ophthalmia neonatorum from gonorrheal infection had already been suggested.

Blanc (1953, 1957, 1959, 1961a) described chorioamnionitis in many important contributions and in great detail; he also coined the descriptive term **amnionic sac infection syndrome**, which is now widely used. Blanc indicated methods for early diagnosis (gastric aspiration of the neonate, touch preparation from amnion), and he clearly explained that this was an ascending infection of the amnionic sac (see also Müller, 1956, and Pisarski et al., 1963, for references to the early European literature). There have been numerous pathologic and clinical studies of this important entity since then (reviewed by Altshuler, 1989; Carroll et al., 1996). It should be mentioned that Genest et al. (1998) introduced the term **pseudovasculitis** for lesions seen in early pregnancy that were, or might be, confused with real inflammation. The lesions described were degenerative in nature. It should be noted that virtually all of their cases were before 20 weeks' gestation,

a time when funisitis is normally not a common feature because the fetus is still sluggish in leukocytic reaction. It goes without saying, then, that "funisitis" is the *fetal* response to infectious agents within the amnionic fluid compartment.

Hallman et al. (1989) have shown that high concentrations of ceramide lactoside are contained in the amnionic fluid of patients with chorioamnionitis. They suggested that the lipid derives from phagocytosing granulocytes. Kirshon et al. (1991) found that patients with prenatal infection had amnionic fluid glucose levels of less than 10 mg/dL. Romero et al. (1987b) showed that arachidonate lipoxygenase products are much elevated in this infection. In a later study, these authors (Romero et al., 1989b) identified as evidence of macrophage activation that infected amnionic fluid contained cachectin-tumor necrosis factor. Biggio et al. (2004) found that elevation of metalloproteinase-8 levels were strong predictors of subsequent prolonged premature rupture of membranes (PPROM). Many other intensive investigations have been published that clarify the role of amnionic sac infection in premature delivery. Importantly, Miyano et al. (1998) showed elevated fetal blood levels of a variety of complement components, lowered albumin, and other protein perturbations in chorioamnionitis. They then correlated these with "stages" of chorioamnionitis and necrotizing funisitis. The latter were thought to have "ended their initial active inflammatory states, but they still have subacute immune activation." Shim et al. (2004) correlated chorioamnionitis with PPROM and suggested that *inflammation* rather than *infection* should be used to designate the state of affairs because in only a limited percentage of their study, organisms were found in the fluid; it must be said, however, that not all possible organisms were attempted to be cultured either. In a subsequent contribution by Kim et al. (2004), specific changes in the expression of "pattern recognition markers," the Toll-like receptors 2 and 4 of amnionic epithelium were found. They suggested that these have a specific function of activating the immune system against very specific antigens. Interestingly, Akinbi et al. (2004) found that vernix caseosa and amnionic fluid normally contains numerous antimicrobial peptides in the absence of chorioamnionitis.

In our opinion, chorioamnionitis is *always* due to infection, and the work of Gibbs et al. (1992) and many others cited below support this notion. The speculations of Dominguez et al. (1960) are unfounded. They described umbilical cord inflammation (funisitis) in 10% of 1000 consecutively studied placentas and portrayed it as being "lymphocytic" (which it practically never is); they related funisitis to prolonged labor and meconium discharge. The complete absence of inflammation in most meconium-stained umbilical cords, the published negative findings of Fox and Langley (1971), and the personal experience of most placental pathologists negate the notion that the common funisitis is caused by hypoxia, as was suggested. Widholm et al. (1963) stated summarily that meconium causes funisitis. It is granted that meconium discharge and funisitis are occasionally combined, but meconium per se is not an inflammatory agent. Maudsley et al. (1966), who presented a good description of the amnionic sac infection syndrome, also insisted that the term be reserved for cases with verified infection. Some other authors have neglected the consideration that fastidious organisms may cause chorioamnionitis (e.g., Olding, 1970). There is thus still lingering doubt and confusion as to the nature of chorioamnionitis (Anonymous, 1989a), but when Arias and colleagues (1993) studied the problem of preterm labor in 105 women, they found that essentially two distinct subgroups exist: those with infection (n = 63) and those with decidual vasculopathy (n = 42). Moreover, Oyarzún et al. (1998) have shown a remarkable increase in identifying the presence of microorganisms in amnionic fluid (46%) when they employed the organisms by polymerase chain reaction than when they attempted culture (12%). They developed a technique to screen for 16 different organisms simultaneously that should be more useful for future studies.

Chorioamnionitis is an acute inflammatory reaction in which PMNLs principally participate. Eosinophils are found at times but only in protracted infections; and macrophages may participate to a variable extent. Plasma cells are generally absent in the membranes, however, except in some of the very chronic infections to be discussed below. The leukocytes come from two sources: the intervillous space (and are then maternal), and fetal surface blood vessels (Fig. 20.7). The emigration of leukocytes is always directional, toward the amnionic cavity, presumably toward an antigenic source. Pankuch and his colleagues (1989) studied this "amniotropism" of infected amnionic fluid. They found it to be a better indicator of infection than Gram stains, culture, or chromatography.

Recently, Fraser and Wright (2002) defined an additional entity. They found 12 cases of single-vessel inflammation **without** amniotropism, and in these cases eosinophils and T cells were the major components. They occurred in term infants without chorioamnionitis and were generally confined to single chorionic (rarely cord) vessels. The cause of this unusual inflammatory process is so far obscure.

In young gestations, especially those prior to the 20th week of gestation, the PMNLs are mainly of maternal origin. By midtrimester, the fetus begins to be capable of producing leukocytes that participate in the inflammatory response to leukotaxins (Müller, 1956). Sampson et al. (1997) found XY chromosomes in over 90% of leukocytes from amnionic fluid aspirates in four pregnancies with male fetuses. Interestingly, the membranes were all unruptured and bacteria were found on smears of the

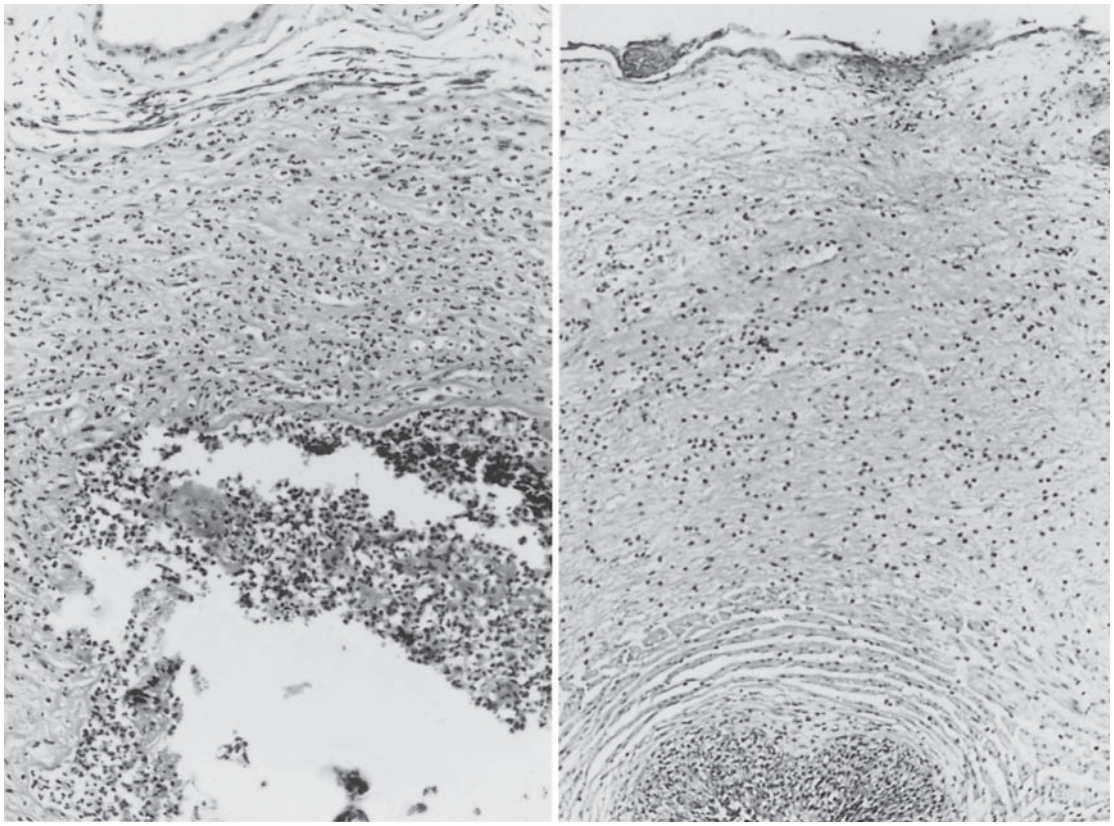

FIGURE 20.7. Placental surface in 30 weeks' gestation delivery. The patient had gonorrhea and her membranes had been ruptured for 40 hours. A 1200-g infant with pneumonia was delivered. Note the exudation of polymorphonuclear leukocytes (PMNLs) from the intervillous space (left), minimal vascular involvement (right), and amnion necrosis. H&E ×240 (left); ×160 (right).

aspirates in two cases. These investigators felt that emigration of leukocytes from maternal vessels was problematic, that emigration from cord vessels was hindered by the rapidity of blood flow, and suggested that leukodiapidesis may occur across fetal pulmonary membranes. That is contrary to the histopathologic findings of most perinatal pathologists. Neonates, when compared to adults, still have reduced leukocyte counts, and their PMNLs are also less capable of ingesting microbes. Premature infants, therefore, may be prone to developing sepsis (Cairo, 1989). We have seen, however, premature infants with white blood cell counts of over 100,000, presumably because of stimulation by specific organisms. The maturation of the fetal lymphocyte system was studied by Berry et al. (1992). Fetuses had significantly fewer $CD57^+$ natural killer T cells, and other age-dependent changes are summarized in this study.

With funisitis, the inflammatory cells emigrate first from the umbilical vein and later from the arteries. They also migrate toward the amnionic surface, and only rarely toward the center of the cord. Many die during the migration. It has been suggested that they rarely reach the amnionic fluid but we believe that this suggestion is incorrect (Anonymous, 1989a). It is common, for instance, to find aspirated PMNLs in lung and stomach of neonates with chorioamnionitis, intermixed with squames. This pus is not produced in the fetal lung, as only late in the infectious process can one find an inflammatory accumulation within the alveolar tissue in response to infection. Pus can also, at times, be aspirated at amniocentesis. The dead inflammatory cells of the placental surface frequently accumulate in large quantities underneath the amnion in the potential space that exists between amnion and chorion (Fig. 20.8).

Experiments designed to identify the reason for the relatively slow permeation of the amnion by leukocytes have suggested that the type V collagen composition of the amnionic basal membrane prevents the ready transgression by PMNLs (Azzarelli & Lafuze, 1987). Some experimental evidence indicates that this amnionic sac infection reduces the strength of the chorion laeve (McGregor et al., 1987; Sbarra et al., 1987; Schoonmaker et al., 1989; Pressman et al., 2002). Sbarra et al. (1985) demonstrated that when membranes are incubated with lysolecithin or phospholipase A_2, their bursting pressure decreases. Membrane "stripping" alone causes the release

FIGURE 20.8. Massive chorioamnionitis in a stillborn at 23 weeks' gestation. Exudate is mostly necrotic and has accumulated in amnion. The placenta had a purulent surface and marked funisitis. Stillborn. H&E ×60.

of this enzyme (McColgin et al., 1993). It might parenthetically be pointed out that the term **amnionitis** is strictly speaking erroneous. The amnion has no blood vessels; thus inflammation, a vascular phenomenon, cannot take place in the amnion. It is only passively possible, by transmigration of leukocytes that originate elsewhere. Gleicher et al. (1979) have identified a blocking factor in the amnionic fluid that enhances leukocyte migration, presumably similar to the material that was studied by Schoonmaker et al. (1989).

The pus may reach the lung, stomach, and middle ears (Fig. 20.9). When chronic aspiration pneumonia occurs, the neonatal lung contains lymphocyte and plasma cell infiltrations. These result from an immunologic recognition of the antigen (Fig. 20.10). Benner (1940) found that 26% of stillborns had middle ear aspiration of pus. A strong correlation exists between chorioamnionitis and otitis. McLellan et al. (1962) found purulent exudate in 19 of 28 temporal bones of neonates weighing between 1000 and 1500 g. The widely patent eustachian tube of premature infants is believed to be a possible portal of entry of this aspirated infected amnionic fluid. Congenital pneumonia has been documented in numerous publications following Ballantyne's (1904) first description. It is correlated with chorioamnionitis and funisitis. Barter (1962) argued in favor of Dominguez' hypothesis of hypoxia as the cause of the inflammation (see letter from Osborn, 1962; see also Aherne & Davies, 1962; Browne, 1962). Anderson et al. (1962), Fujikura and Froehlich (1967), and Steiner et al. (1961), among many authors who studied the phenomenon, found that the "drowning in pus" correlates with chorioamnionitis, prematurity, and premature rupture of the membranes, and in long-standing infections, some plasma cell component may be found (Fig. 20.11). Some of the necrotic exudate underneath the amnion may ultimately calcify, but the fetus is usually delivered before this happens. Simon et al. (1989) undertook bacteriologic studies of infants born after premature rupture of membranes. They found that 26% had the same bacteria in placental arterial blood, ear swabs, and meconium, the predominant organisms being *Escherichia coli*, *Bacteroides fragilis*, and streptococci. A significant study of the nature of organisms that cause chorioamnionitis comes from Hillier et al. (1991). The organisms most frequently associated with preterm delivery and chorioamnionitis were group B *Streptococcus* and *Fusobacterium*; *Peptostreptococcus* was related only to preterm delivery, whereas *E. coli, Bacteroides*, and *Ureaplasma* were significantly related only to chorioamnionitis. Formerly considered to be a *Bacteroides* species, *Capnocytophaga* sp. is a newly recognized cause of severe chorioamnionitis. This gram-negative anaerobic organism is a common cause of periodontal disease and, not surprisingly, ascending infection leading to chorioamnionitis has followed oral sex (Edwards, et al., 1995; Hansen et al., 1995; Mikamo et al., 1996).

The fetal surface vessels partake in the inflammatory response to the leukotaxin, but generally little happens here before the 20th week of gestation. The maternal component of the leukocytic reaction originates in the intervillous space and in the maternal vessels of the decidua in the free membranes (Fig. 20.12). Even in dichorionic twin placentas, some exudate may be found in a part of the dividing membranes, where the PMNLs originate from persisting maternal vessels (Fig. 20.13). In this maternal response to amnionic sac infection, leukocytes first marginate beneath the fibrin under the chorionic plate. They then infiltrate the chorion and eventually the amnion. The subchorial accumulation has been designated "intervillositis," an unfortunate but often used term. It is true that other types of intervillositis occur (vide infra), but these are more chronic processes and they differ substantially from the acute infections. Infectious organisms are rarely seen in the intervillous space,

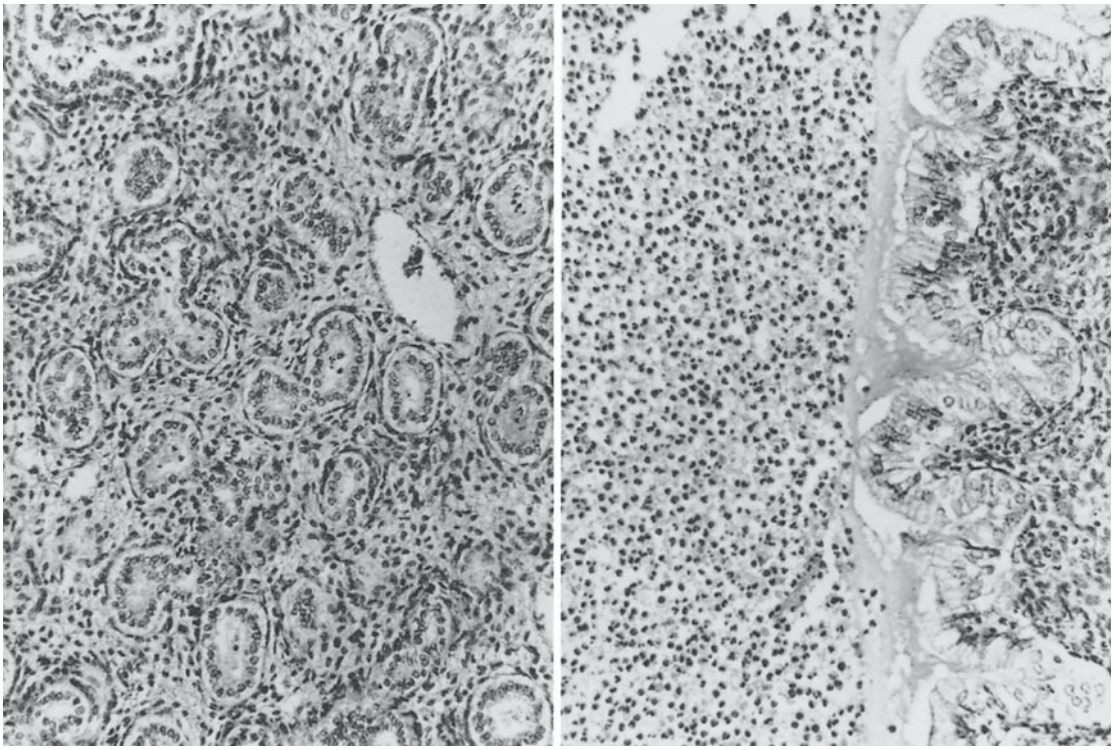

FIGURE 20.9. Aspiration of amnionic fluid pus in the still tubular alveolar spaces of a 16 weeks' gestation fetus (left) and stomach (right). H&E ×120.

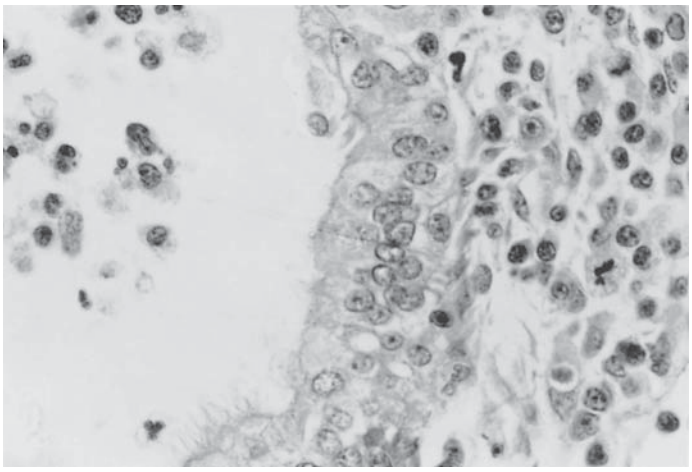

FIGURE 20.10. Chronic aspiration pneumonia in a stillborn. Note the pus in the bronchial lumen and plasma cells in the interstitial parenchyma. H&E ×160.

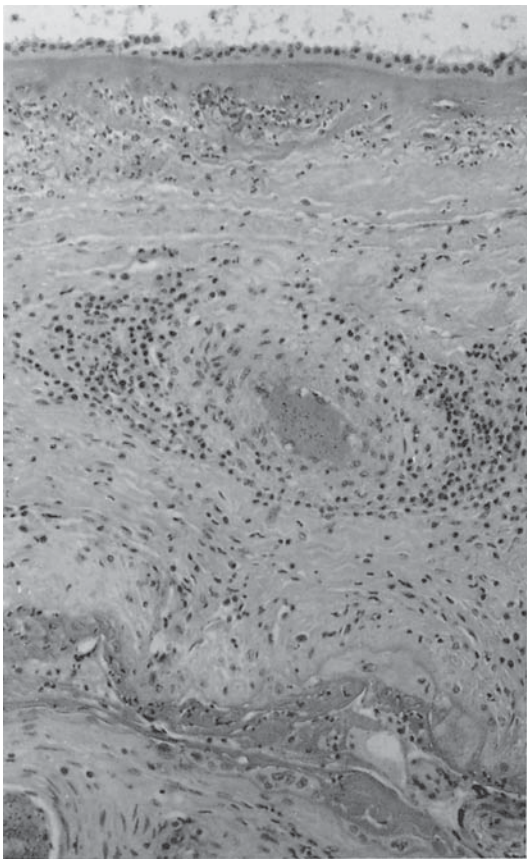

FIGURE 20.11. Placental surface at 28 weeks' gestation with chronic inflammation (plasma cells). H&E ×60.

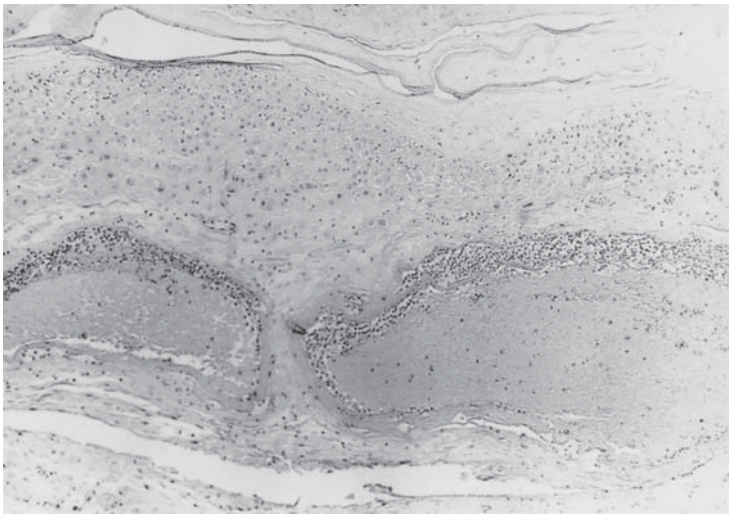

FIGURE 20.12. Placental membranes at term with early inflammation. Leukocytes are accumulating in maternal vessels, with direction toward the amnionic surface. Mural thrombosis is beginning. The patient was febrile, and funisitis was present. H&E ×60.

although toxins may accumulate here. In acute chorioamnionitis the leukocytes merely react to the leukotactic signal that has permeated through the placental surface; they then accumulate in the subchorial space and finally migrate. Abscess formation underneath the chorionic plate and dissemination of exudate between villous trunks are rare (Vernon & Gauthier, 1971). When it is present, one must consider congenital listeriosis and *Campylobacter* sp. infection first; other infections are much less frequently the cause. With listeriosis, villous and intervillous abscesses occur frequently (vide infra). Intervillous abscesses occur occasionally in maternal septicemias. We have seen them with maternal staphylococcal and *E. coli* infections. The mothers are usually so ill that labor and delivery occur before abscesses develop. Indeed, staphylococcal infection has only rarely been reported. Negishi et al. (1998), who described such a case, found only one previous report. Their patient was at 38 weeks and mild fever (37.8°C) was noted, but the membranes were intact. She had been treated with chloramphenicol for bacterial vaginosis. The fetus died suddenly. Cord blood and placental surface grew *Staphylococcus aureus*, and there was chorioamnionitis. Levy (1981) believed that a placental abscess he discovered could be the cause of the maternal fever. This abscess occupied 25% to 39% of the placental surface in a term pregnancy, but no bacteria were isolated, and listeriosis was not ruled out. Another placental abscess was due to *Proteus mirabilis* infection in a febrile patient, gram-negative bacilli being present in sections (Ravid & Toaff, 1976). In another pregnant woman an intravenous line had been placed at 12 weeks' gestation as treatment for hyperemesis. She developed *Serratia* sepsis and was appropriately treated. When she delivered at 34 weeks, an old abscess without organisms was identified in the placenta. Bendon et al. (1998) reported on two fetal deaths due to placental abscesses from maternal *E. coli* sepsis with disseminated intravascular coagulation (DIC). There was focal infarction around the abscesses,

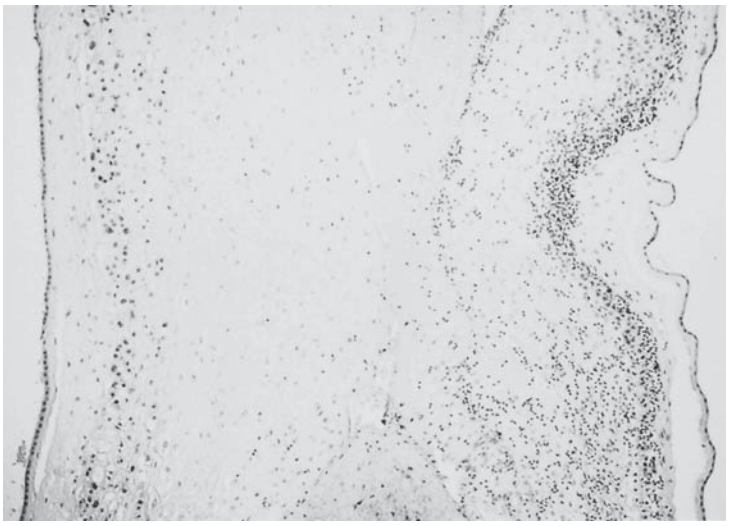

FIGURE 20.13. Dividing membranes of a diamnionic/dichorionic (DiDi) twin placenta with inflammation in the right sac. H&E ×25. (Courtesy of Dr. S.G. Driscoll, Boston.)

but chorioamnionitis was absent. **Villous** abscesses occur, as was reported, after intrauterine transfusion with infected blood (Scott & Henderson, 1972). The villi are otherwise almost never involved in common cases of chorioamnionitis, however severe that process may be. Subchorionic fibrin deposits are excellent sites from which to culture bacterial organisms, according to Aquino et al. (1984). These authors preferred to sample this site because it is not contaminated with vaginal organisms and because they experienced good recovery of bacteria from these specimens. They isolated group B hemolytic streptococci, anaerobic cocci, and "rods," organisms that commonly cause endometritis, pelvic infection, and neonatal sepsis.

The exudate in funisitis may occasionally be visible macroscopically (Fig. 20.14). It must be emphasized, however, that funisitis (umbilical vasculitis) does *not* signify the existence of fetal sepsis, as is often believed. It *does* signify the presence of a fetal inflammatory response, however. Blanc (1961a) has specified the possible means by which fetal sepsis can take place. It is a relatively late event in the course of prenatal infection with bacteria. Blanc opined that fetal sepsis may result from invasion of organisms through lung and intestinal tract.

Prior to the delineation of the amnionic sac infection syndrome, funisitis was thought to be primarily related to congenital syphilis, and spirochetes were usually sought from endothelial scrapings by darkfield examination. This association is now no longer held to be firm (reviewed by Beckmann & Zimmer, 1931). With funisitis, the leukocytes marginate first at the vascular intima and then begin to dissect among the muscle bundles of the umbilical vein and arteries, finally infiltrating Wharton's jelly (Fig. 20.15). They also reach the cord's surface and may accumulate there in substantial numbers. The fetal PMNLs have the same fine-structural features as those from adults. When they emigrate through the umbilical vein wall, degeneration of its inner elastic components is observed (Fig. 20.16). With some infections, notably that with *Candida albicans*, small accumulations of PMNLs are seen on the cord surface. They are often visible macroscopically and have a typical, granular appearance. Old exudate in the cord may accumulate in concentric perivascular rings, giving the appearance of Ouchterlony immunodiffusion plates (Fig. 20.17). This old exudate is more prone to developing mineralization than is the exudate of the fetal surface of the placenta. In fact, this calcification may reach extraordinary proportions at times, so that the cord cannot be clamped readily (vide infra). It is then referred to as necrotizing funisitis.

The microorganisms that have caused the inflammatory response may be seen in many infected placentas, particularly in cases of listeriosis, candidiasis, fusobacterial infection, and some of the infections with common cocci. But many cases of chorioamnionitis result from infection with organisms that are not so readily demonstrated histologically or that are not commonly considered. Examples include *Chlamydia* (Andrews et al., 2000) and *Mycoplasma* and *Ureaplasma* (Lu et al., 2001; Yoon et al., 2003). Mural thrombosis in chorionic vessels is frequently present when the infection has been of longer duration (see also Arias et al., 1997). It begins at the intima of veins, usually toward the amnionic surface, and gradually increases (Fig. 20.18). The thrombi may be grossly apparent as yellow-white streaks, and eventually the villous tissue of the involved vessels atrophies. In the umbilical cord, thrombi have a less characteristic macro-

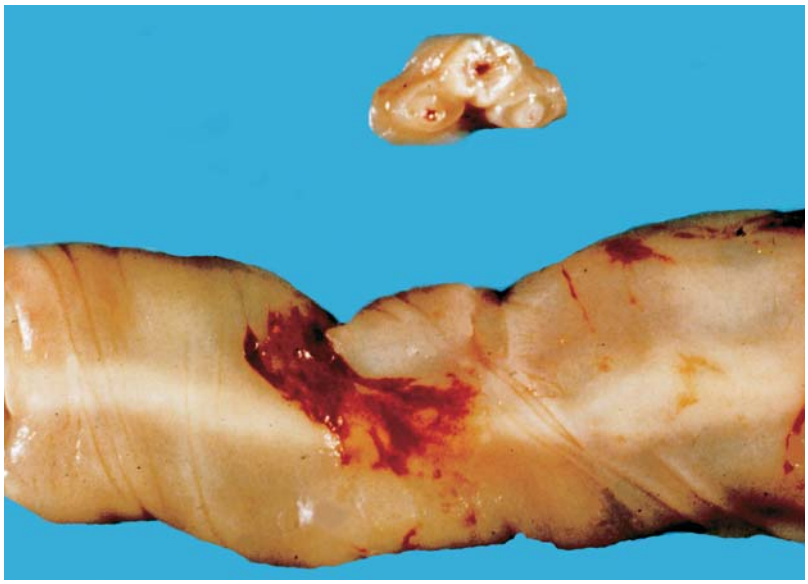

FIGURE 20.14. Longitudinal and cross section of an umbilical cord at 30 weeks' gestation. The patient had no fever. A yellow streak was seen along the umbilical vein, and the cord appeared brownish. There is a prominent white ring of acute inflammatory exudate around the umbilical vein.

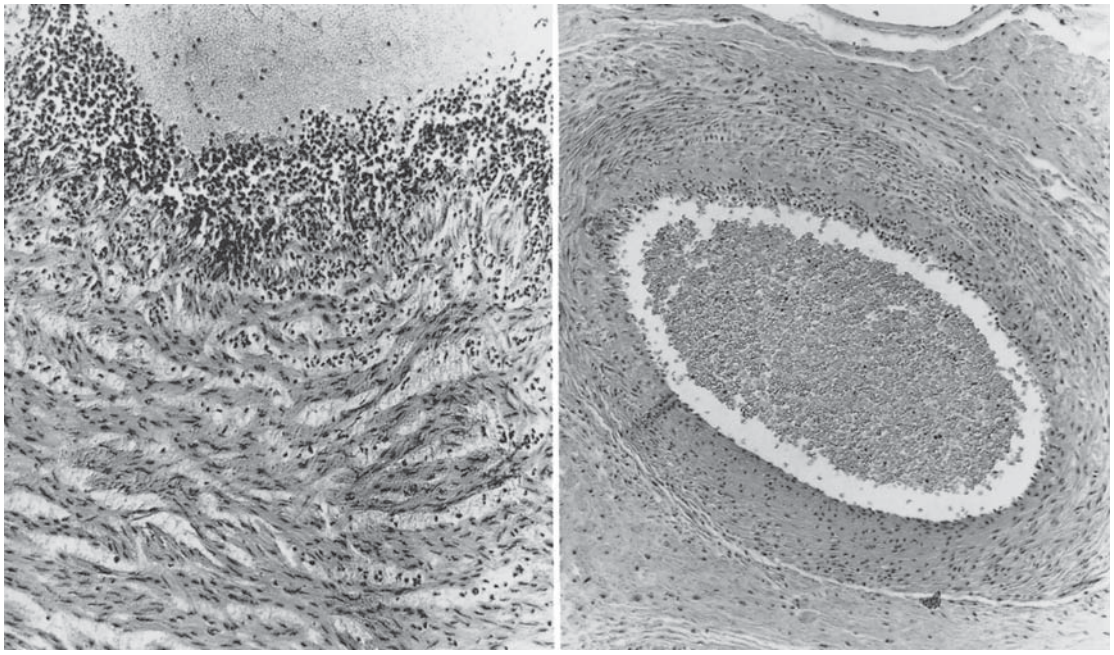

FIGURE 20.15. Umbilical phlebitis (left) and arteritis (right). Leukocytes are penetrating between muscle bundles toward the cord surface. H&E ×260.

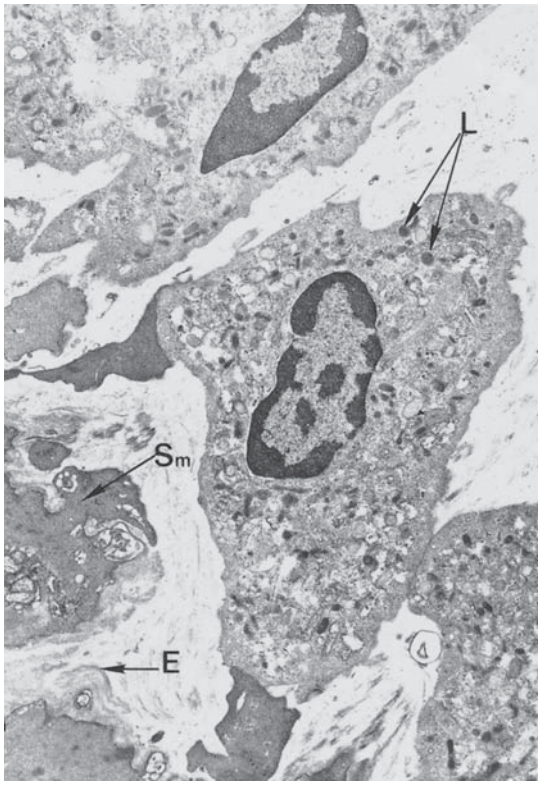

FIGURE 20.16. Electron micrograph of a polymorphonuclear leukocyte in the process of emigrating through an umbilical vein. Mature pregnancy, prolonged rupture of membranes. L, lysosomes; SM, smooth muscle cell; E, degenerating elastic membrane. ×9000. (Courtesy of Dr. G. Altshuler, Oklahoma City, Oklahoma.)

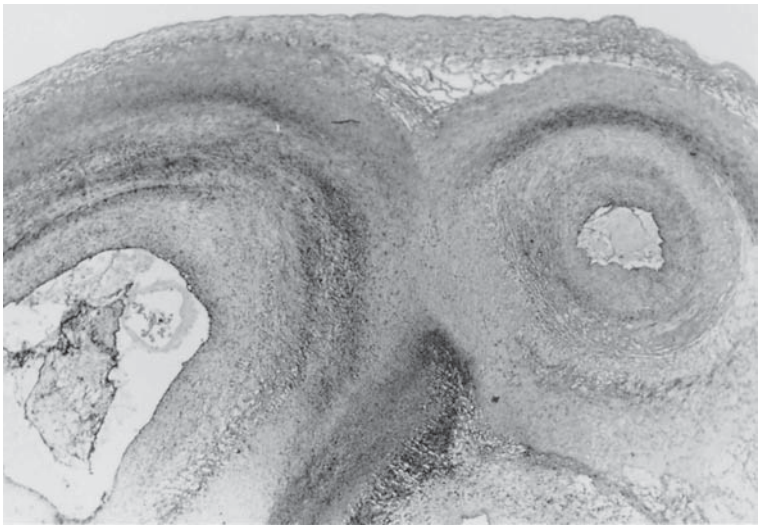

FIGURE 20.17. Chronic funisitis with rings of exudate, some of which are degenerated, around cord vessels. Small for gestational age (SGA) infant near term; no villitis. H&E ×40.

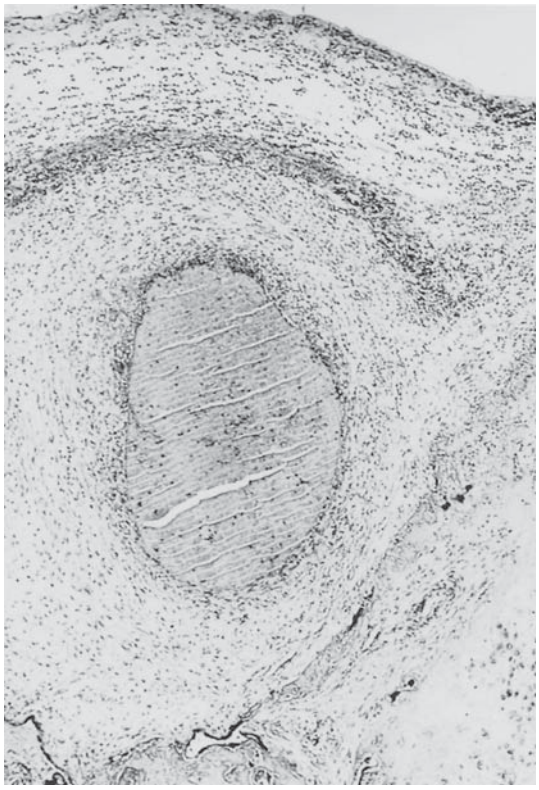

FIGURE 20.18. Long-standing chorioamnionitis and vasculitis of chorionic vessels at 26 weeks' pregnancy. The darker ring of exudate is degenerating, as is the amnionic epithelium. Early mural thrombosis is present at the surface of the vein. Malodorous placenta, 4 days premature rupture of membranes (PROM), 900-g infant. H&E ×20.

scopic appearance but may also involve arteries (Fig. 20.19). It is true, though, that most thromboses of large placental vessels have another etiology, mostly being secondary to obstruction of venous return. Finally, in the

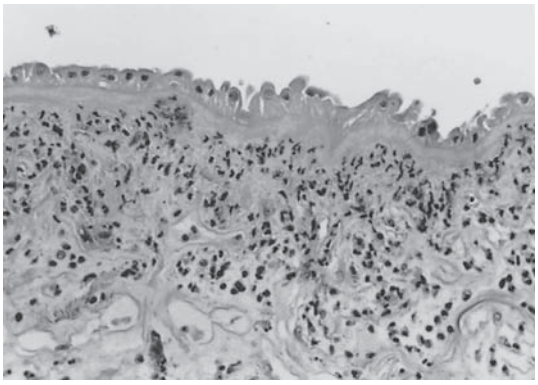

FIGURE 20.20. Chorioamnionitis associated with amnion necrosis. H&E ×160.

amnionic infection syndrome, the amnionic epithelium is frequently degenerated, especially in areas of severe inflammation (Fig. 20.20). Thrombosis of umbilical veins is rarely reported, and it is summarized by Wolfman et al. (1983), who saw it in a surviving neonate. It was associated with marked inflammation. These authors also review the sparse literature and draw attention to the greater frequency in diabetic gestations.

Chorioamnionitis is common. Fox and Langley (1971), for instance, found it in 24.4% of 1000 consecutive livebirths. A study of Salafia et al. (1989) showed that some degree of chorionitis was present in 4% of uncomplicated term deliveries; in 1.2% the chorioamnionitis was "clinically silent." Inflammation of membranes and cord is much commoner still in the immature organs of spontaneous, premature births and in patients with premature rupture of membranes. Hillier et al. (1988) found infection in 67% of preterm deliveries, compared with 21% of term gestations. Guzick and Winn (1985) did a prospective study of 2774 women and found the overall incidence

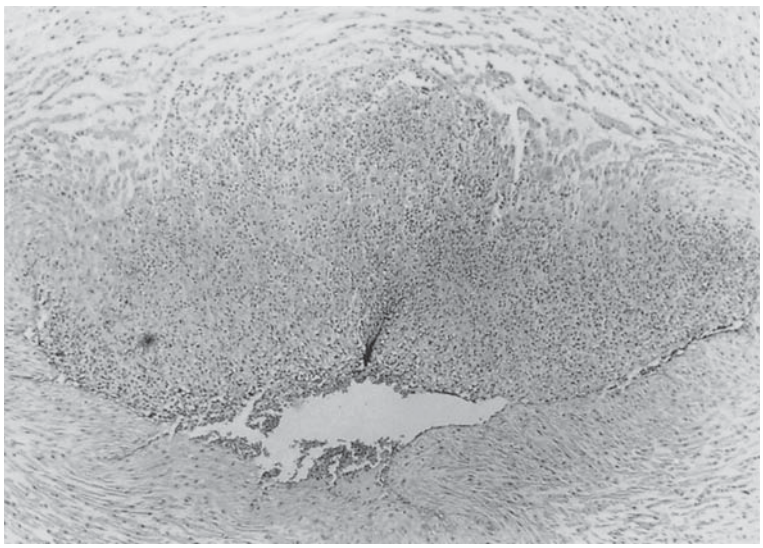

FIGURE 20.19. Organized, partially occlusive arterial thrombus in an umbilical artery, associated with arteritis. Infant developed cerebral palsy. H&E ×20.

of prematurity to be 5.4%. It was 11% when chorioamnionitis was present without membrane rupture, but 56.7% when premature rupture of membranes and chorioamnionitis coexisted. The authors concluded that 25% of premature deliveries were attributable to chorioamnionitis. Newton et al. (1989) showed in a large study that "duration of membrane rupture [was a] significant risk factor for intra-amniotic infection." The outcome of pregnancy in 59 patients with rupture of membranes before 26 weeks' gestation was studied by Bengtson et al. (1989). They ascertained chorioamnionitis in 45.8% (49.1% perinatal mortality) but also found that "there was a tendency for patients with extremely long latent periods to have lower rates of infection." Holcroft et al. (2004) found that chorioamnionitis and funisitis were not responsible for metabolic acidosis in preterm fetuses and that factors other than hypoxia (mostly culture positive infection) must be responsible for the frequent central nervous system (CNS) damage seen (see also Holcroft et al., 2004). Numerous other investigators have shown that chorioamnionitis is a significant risk factor for prematurity, CNS damage, fetal/neonatal sepsis, and fetal demise (deAraujo et al., 1999; Hansen & Leviton, 1999; Goldenberg et al., 2000; Yoon et al., 2001; Genen et al., 2002; Slattery & Morrison, 2002; Graham et al., 2004; Rouse et al., 2004). Duggan et al. (2001) showed that brain injury is more likely to occur in chorioamnionitis when fetal circulating levels of tumor necrosis factor-α (TNF-α) and interleukins (IL-1β, -6, and -10) as well as $CD45RO^{+}T$ lymphocytes are elevated (see also Cooper & Nuovo, 2005). Patrick et al. (2004) have created a guinea pig model to study the CNS effects of chorioamnionitis. Quintero et al. (1998) sought to assess and "cure" premature rupture by endoscopic study. They identified the funnel-like site of rupture and unsuccessfully attempted "amniopatching" by application of platelets and cryoprecipitate. More recently, the same investigators placed a collagen membrane patch over the rupture site in a patient, thus prolonging the pregnancy by 2 weeks (Quintero et al., 2002).

Many attempts have been made to "grade" the inflammatory process, with the hypothesis that different severities of inflammation might correlate with neonatal outcome and possibly other parameters. This has been only minimally successful, but a study by Redline et al. (2003) showed reasonable reproducibility among a number of pathologists judging placental inflammatory lesions. Not taken into consideration was a study by Ohyama et al. (2002) that suggested the existence of a subacute form of chorioamnionitis, a form that is especially marked by amnion necrosis and that was an infection they felt to be of longer duration. These authors showed that the neonatal outcome was worse with this form of inflammation, especially from a chronic respiratory point of view. Several investigators have shown that the effect of funisitis (arteritis and phlebitis has a greater impact when merely membranitis is present (Kim et al., 2001; Mittendorf et al., 2003). Miyano et al. (1998), who assessed the cord blood levels of various protein components, came closer to a useful means of subdividing the degree of inflammation. Then there are observations such as, for instance, a case of massive chorioamnionitis, funisitis with necrotizing features and severe edema, neonatal white blood cell count of 100,000 at 26 weeks' gestation, and an apparently healthy neonate who survived; conversely, minimal inflammation associated with group B streptococcal infection can be devastating. These and many similar experiences make us believe that the most important features of ascending infection are the type of infectious agent and perhaps the time of onset, but not the degree or the precise nature of the inflammatory response. *Trichomonas*, for instance, can be enormously leukotactic yet have little effect on neonatal morbidity, whereas it is associated with low birth weight and preterm delivery (Cotch et al., 1997). Conversely, group B streptococcus may prevent leukocyte migration and have a devastating effect on fetal/neonatal life. Thus, the extensive investigations on grading the inflammatory response by van Hoeven et al. (1996) and de Araujo et al. (1994), among other such studies, should be interpreted with this caution in mind.

The ascending nature of this infection is signaled by three pathologic findings, but is also supported by culture of intact sacs: (1) There is usually severe, acute deciduitis associated with the membranitis, and it often exceeds the degree of chorioamnionitis (Fig. 20.21). (2) When the intrauterine position of twins is known, including the location of the partition of their amnionic sacs, it is invariably twin A who has chorioamnionitis or whose membranes are more severely inflamed (see Figs. 20.2 and 20.3). (3) When membranes are rolled in such a manner as to have the point of spontaneous rupture on the inside, the degree of inflammation is most significant in the inner portions of the roll, that is, in the proximity of membrane rupture (Figs. 20.22 and 20.23) (Benirschke & Altshuler, 1971). It should be noted, however, that maternal fever **alone** is a poor indicator of the presence of chorioamnionitis, as many patients do not exhibit elevated temperature and others may have an intercurrent infection of other kinds.

It is well known that attempted abortion with nonsterile instruments is frequently followed by sepsis and chorioamnionitis (Studdiford & Douglas, 1956), but chorioamnionitis has also repeatedly been found with unruptured membranes (e.g., Miller et al., 1980b). A good example is the case of (amnionic fluid infection—"chorioamnionitis," according to the authors) with the uncommon organism *Eikenella corrodens* (Jeppson & Reimer, 1991). The 31-week gestation infant remained uninfected, perhaps because of prenatal antibiotic therapy when the

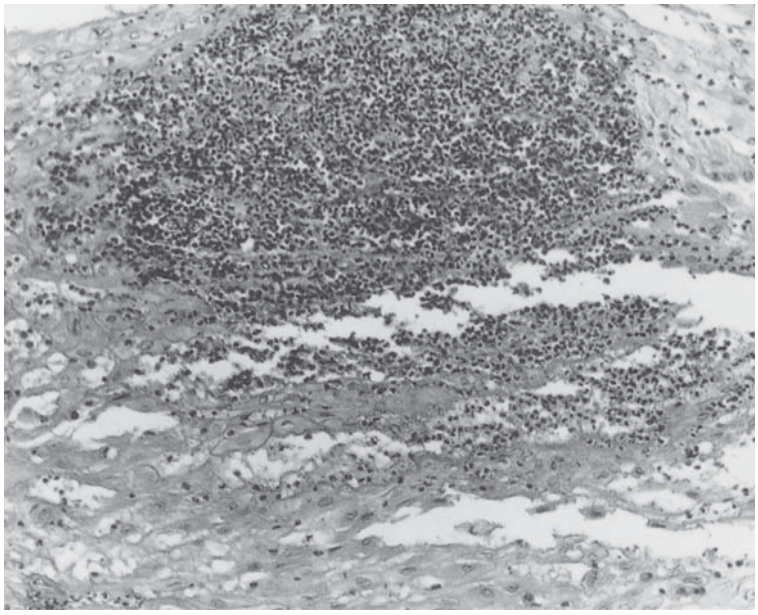

FIGURE 20.21. Acute and chronic deciduitis (decidua capsularis) in an immature placenta with chorioamnionitis. H&E ×160.

Gram-negative rods were identified by culture from amniocentesis. The association of prenatal infection with intact membranes is easiest to show with the relatively common *C. albicans* infection of the amnionic sac. Further, Gyr et al. (1994) showed that, experimentally, *E. coli* organisms could penetrate viable intact placental membranes, with simultaneous changes in glucose and lactate concentrations. Also, many cases have been described in which chorioamnionitis, with or without fetal pneumonia, existed in the presence of intact membranous sacs (en caul). Although this is an uncommon occurrence, it is an important finding for our understanding of the pathogenesis of infection (Royston & Geoghegan, 1985). The general experience that inflamed membranes usually rupture prior to delivery does not argue against the fact that chorioamnionitis can exist with an intact sac. The loss of membrane integrity, resulting from inflammation, makes rupture a probability (Schoonmaker et al., 1989). Numerous reviews exist on this topic (Altshuler, 1984).

The predominant opinion now is that amnionic sac infection is a primary cause of premature rupture of membranes and premature labor, at least in those pregnancies that terminate spontaneously before 30 weeks' gestation (Garite & Freeman, 1982; Toth et al., 1988). This is also our opinion, and we believe that this is the most important unresolved problem in gestation, the reason

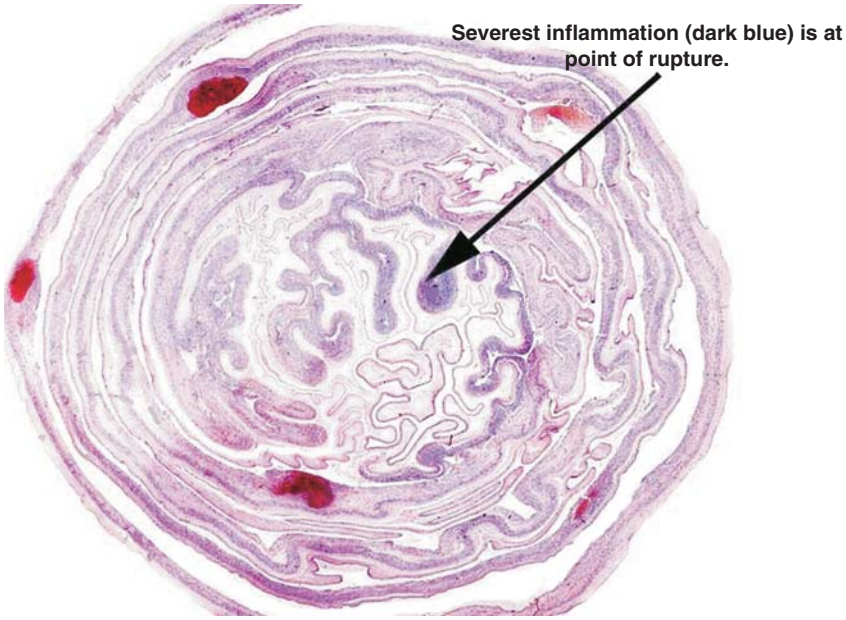

FIGURE 20.22. Membrane roll of placenta with marked chorioamnionitis. The edge of the spontaneous membrane rupture is in the center. Note the dark exudate in the decidua and chorion in the center. H&E ×12.

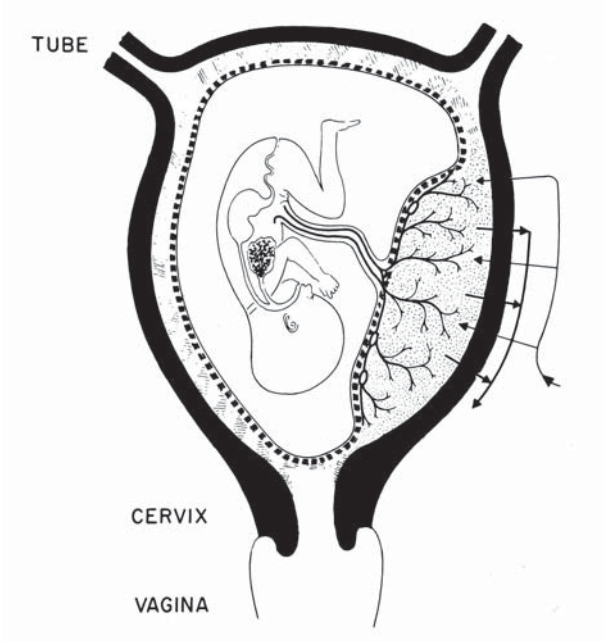

FIGURE 20.23. Intrauterine position of fetus and placenta. Infectious organisms ascend through an opened endocervical canal. They first infect the membranes that cover the internal os and then penetrate into the amnionic cavity.

being that it not only is often recurrent (Mercer et al., 1999; Lee et al., 2003), but also leads to the most premature infant deliveries, of infants who are difficult to treat and many of whom develop cerebral palsy (Wood et al., 2000; Yoon et al., 2000; Kumazaki et al., 2002a). There is also evidence that these infections have an important role in the causation of stillbirths and neonatal deaths (Quinn et al., 1985). The formerly held idea that chorioamnionitis might protect the neonate against developing hyaline membrane disease by the attending stress was invalidated by the controlled clinicopathologic study of Dimmick et al. (1976).

To make the clinical diagnosis of chorioamnionitis may pose problems for the clinician, as only some gravidas experience fever, uterine tenderness, or fetal tachycardia with amnionic sac infection. Bobitt et al. (1981) aspirated amnionic fluid for culture from women in premature labor and found microorganisms in 25%. Seven of eight patients went into labor within 48 hours, and 75% of positive women had no fever. These authors also advocated Gram stains for rapid diagnosis of organisms, a method found to be helpful in the management of patients with premature rupture of membranes and chorioamnionitis (Broekhuizen et al., 1985). Others have advocated the use of gas-liquid chromatography for the early diagnosis of the amnionic sac infection syndrome (Gravett et al., 1982; Wagner et al., 1985; Romero et al., 1988b). This rationale was based on the detection of short-chain organic acids, which are the by-products of bacterial metabolism. Romero et al. (1989e) found that this method is insensitive, especially when gram-negative organisms cause the infection, which is why Pankuch et al. (1989) suggested the use of leukotaxis studies. Maternal pyrexia and leukocytosis are also unreliable predictors, as has been found in numerous studies, and now fibronectin assays seem to be more profitable.

Hawrylyshyn et al. (1983) found that elevated C-reactive protein (CRP) levels correlated better with infection than did maternal fever. Elevation of CRP levels in maternal serum, advocated by Evans et al. (1980) as a means to predict chorioamnionitis, has also not been universally helpful. Farb et al. (1983) identified two patients with verified infection and normal levels; false-positive results were also obtained. Ernest et al. (1987) reported problems of both false-positive and false-negative levels. Watts and her colleagues (1993) found that elevated CRP levels were useful in deciding when to do cultures of amnionic fluid but they found poor correlation with chorioamnionitis. Other investigators, however, have found excellent correlation with CRP levels and chorioamnionitis and have advocated its use in the clinical setting (Romem & Artal, 1984; Ismail et al., 1985; Potkul et al., 1985).

Because of the importance of this ascending infection, investigators have sought new means of predicting the existence of chorioamnionitis before birth. Egley et al. (1988) suggested that amnionic fluid esterase levels (derived from PMNLs) have high specificity (100%) and sensitivity (81%). But, as in bacterial studies of cerebrospinal fluid (CSF), lactate, esterase, etc. are no more sensitive than looking for PMNLs from which they are derived. A Gram stain takes 5 minutes to perform and may be much more useful. Ohlsson and Wang (1990) reviewed 39 studies and concluded then that "an ideal test to predict chorioamnionitis or neonatal sepsis was not found."

Romero et al. (1987a, 1988a) and Cox et al. (1988) found that quantitation of the lipopolysaccharide component of Gram-negative organisms (endotoxin) might be used for identification of these infections. Both groups of investigators found elevated levels of endotoxin in specific infections with the *Limulus* test; and when the test was combined with Gram stains, a more adequate means of prenatal diagnosis seemed possible. A variety of kinins, especially IL-1 and TNF were next being investigated as possible prime movers in initiating uterine contraction (Romero et al., 1989a,b; see reviews by Mitchell et al., 1993; Oláh et al., 1996; Kayem et al., 2004). In one of the few studies of cervical mucus (which we consider to be of great importance in uterine defense mechanisms), Platz-Christensen et al. (1993) found that concentrations of endotoxin and IL-1α are significantly increased in vaginal fluid and cervical mucus of women with bacterial vaginosis. The primacy of cervical problems in ascending infection was related by Iams (1998), and Leppert (1998) sought cleavage of cross-linked collagen fibers as a pos-

sible early mechanism for cervical dilatation. We found markedly increased amounts of IL-1 and IL-1ra in several areas of placentas with chorioamnionitis (Baergen et al., 1994), indeed we believe that the principal problem is the absence of endocervical protective mucus. It is impressive to observe the quantity of this viscous mucus in the endocervical canal of hysterectomy specimens done for placenta percreta, and in animals that succumb during pregnancy at the San Diego Zoo from trauma or other unrelated causes. Moreover, Hein et al. (2001, 2002) in two excellent studies of the human endocervical mucus have shown its richness in defensive molecules and cells (Fig. 20.24). Genc et al. (2004) have measured the IL-1ra and IL-1β response in vaginal/cervical secretions and found that in women with various pathogens, the ratio of IL-1ra/IL-1β was decreased and was associated with preterm delivery. Similar observations of a decreased immune function of cervical secretions and subsequent chorioamnionitis were made by Simham et al. (2003).

Many other studies have since been conducted to further characterize the cytokine involvement of prenatal infection and premature labor (see review and new findings in Arntzen et al., 1998). Lockwood et al. (1994) found increased cervical IL-6 levels to be poor indicators of maternal infectious sequelae, whereas Coultrip et al. (1994), Andrews et al. (1995), and Yoon et al. (1995) described how amniotic fluid IL-6 levels are useful as rapid diagnostic tests to predict premature labor with intact membranes. Menon et al. (1995) determined that the amnion and chorion are the sites of inflammatory cytokine (IL-1 and IL-6) production when they sought these by messenger RNA detection (see also Reisenberger et al., 1998). In a later contribution, Yoon et al. (1997a,b) suggested that IL-6 and IL-1β or TNF-α may "play a role in the genesis of brain white matter lesions" in infants delivered with chorioamnionitis (see also Grether & Nelson, 1997). Stretching alone of the membranes was sufficient to release IL-8 and collagenase activity (Maradny et al., 1996). IL-8 and IL-10 were incriminated as participants in premature labor by Osmers et al. (1995) and Greig et al. (1995), whereas IL-1α was found to be elevated in studies by Dudley et al. (1996). Conflicting results concerning the cellular origin of many cytokines have been published. Thus, Reisenberger et al. (1998) found cultured amnion cells to produce IL-6 and IL-8 upon bacterial exposure; Steinborn et al. (1998) found the origin of TNF-α to be placental macrophages, whereas IL-1 and IL-6 came from placental endothelial cells. It is also of interest that women who had chorioamnionitis in an earlier gestation had significantly higher levels of TNF-α production after lipopolysaccharide stimulation than controls (Amory et al., 2001). It can thus be seen that the precise pathophysiology of the mechanism of premature labor and infection and the participation of various membranes and locales of cytokine production are under active study, without a final, agreed-upon resolution still forthcoming. Clearly, infection and inflammation are the most important aspects in the process. Most appealing to us, having long assumed that cervical/endocervical "competence" is an important aspect in preventing ascending infection, is the finding by Svinarich et al. (1997; also Quayle et al., 1998) that normally the endocervix is a rich source of defensin-5. This protein plays an important protective role against infection in other organs (bowel) and may become a significant player in the future. At present, the cervical/vaginal presence of elevated fibronectin levels seems to be the most practical way of monitoring progression of chorioamnionitis (Bartnicki et al., 1996; Garite et al., 1996; Rizzo et al., 1996; Goldenberg, 1997; Sennström et al., 1998). Simhan et al. (2004) have added elevated vaginal pH and neutrophils to this array of tests for PPROM, as it is now referred to. These tests have been commercially marketed and are highly successful in predicting delivery within a week (Peaceman et al., 1998). The fibronectin detected is thought to derive from the membranes.

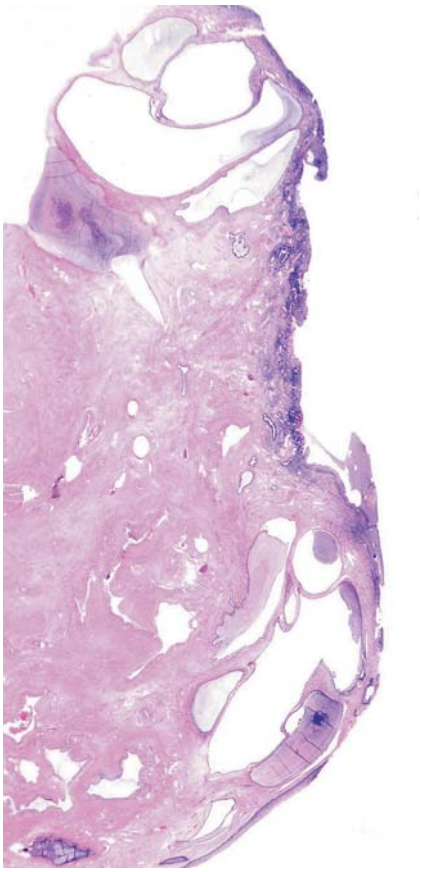

FIGURE 20.24. Endocervix of uterus from cesarean section for placenta percreta at 37 weeks' gestation. Thick purple mucus fills the canal and interdigitates with the mucus glands.

Because labor is readily induced with prostaglandins, they have been studied as the possible main mediators of

the preterm labor associated with chorioamnionitis. Although prostaglandins are well-known mediators of many aspects of disease, and they are also the chemicals that have proved to be useful in initiating labor, there are reservations about their primacy in the initiation of normal labor. While seeking a possible link between premature labor and placental inflammation, we found that arachidonic acid was consumed in the process of labor (Curbelo et al., 1981). The testing was done by chromatography of phospholipids from placental membrane extracts obtained from various types of delivery. Arachidonic acid appeared to be electively stored in the amnion. Later, a large number of microorganisms were tested for phospholipase activity because initiation of labor was believed to result from phospholipase A_2 activation and because of its association with infection. It was then found that many organisms contain this enzyme in considerable quantities (Bejar et al., 1981; McGregor et al., 1991). This observation led to the hypothesis that bacterially mediated enzymatic conversion of arachidonic acid may signal the onset of premature labor in pregnancies complicated by chorioamnionitis. Others have since studied many more organisms and found that phospholipase is liberated from a large number of microorganisms, with release of prostaglandin from amnion (Lamont et al., 1990). Bennett and Elder (1992) found that bacterial infection cannot initiate labor from "intrinsic biosynthesis and release of prostaglandins . . . by the bacteria themselves." We now believe that there is an insufficient quantity of lipase to come from the usually relatively small number of bacteria to initiate and maintain labor. Rather, the enzyme is more likely being provided by the large number of leukocytes that are also known to possess phospholipase (Victor et al., 1981) and whose enzyme is activated by chemotactic peptides (Galbraith, 1988). The lipase also occurs in high concentrations in the placental membranes (review by Vadas & Pruzanski, 1986; Kredentser et al., 1995; Skannal et al., 1997). Okita et al. (1983) identified substantial stores of arachidonic acid in human amnion and concluded that it originates from amnionic fluid.

Lamont et al. (1985) also exposed amnion cells in culture to bacterial products and found prostaglandin E to rise markedly as a result. They thus affirmed that chorioamnionitis may cause premature labor. This finding was amplified by Bennett et al. (1987), who performed similar experiments. A correlation between chorioamnionitis and premature labor is additionally supported by findings of significantly elevated prostaglandin levels in infected amnionic fluid (Romero et al., 1986) and by the demonstration of markedly increased prostaglandin production from infected amnion (Lopez Bernal et al., 1987).

Despite these attractive findings of prostaglandin metabolism, attention has been paid to the increase of amnionic leukotriene concentrations during labor (Romero et al., 1988c) and to the decidual IL-1 production during premature labor (Romero et al., 1989a,f) as well as many other proteins. Deciduitis, decidual macrophage activation, and PMNL exudation, in particular, play an important role in the initiation of premature labor. It must be admitted, however, that although the evidence of infection as a primary cause of chorioamnionitis and of premature labor is no longer in doubt, the precise chemical cascade that ultimately leads to myometrial contractions is not yet elucidated. A multifactorial mechanism for preterm membrane rupture is advocated by Parry and Strauss (1998). They reviewed the large literature and paid special attention to the loss of strength of the placental membranes. Further, the primacy of infection is supported by the meta-analysis of seven studies on prophylactic antibiotic therapy in premature rupture of membranes (Egarter et al., 1996). It indicated reduced neonatal morbidity from infections in mothers with premature rupture of membranes (PROM) treated prenatally with different antibiotic regimens. A comprehensive review, especially concerning prevention and therapy of bacterial vaginosis, premature delivery and PROM comes from McGregor and French (1997). Regrettably, metronidazole treatment to prevent premature delivery in women with bacterial vaginosis did not reduce its occurrence, nor did this therapy prevent preterm delivery from trichomonas infections (Klebanoff et al., 2001).

Many investigators have graded the inflammatory infiltration (e.g., Thiery et al., 1970; Naeye et al., 1983) so as to perhaps correlate it with clinical findings, foe example, rupture of membranes and maternal fever. We have found this to be impractical for several reasons. For instance, there are severe prenatal infections with some types of organisms, in particular the group B streptococcus, that elicit little placental inflammatory reaction but that can produce devastating disease in the newborn. It is also likely that different organisms have differing ability to penetrate the membranes. This point was shown experimentally by Galask et al. (1984), who exposed membranes to bacterial cultures. They found that group B streptococci penetrated membranes more readily than did coliform bacilli and gonococci. We believe that the intensity of inflammation is more closely related to the nature of the organism, rather than to the chronicity of the infection. It seems also difficult to estimate how long the infection has been active. This uncertainty has hindered acceptance of the opinion that membrane rupture *follows* membranitis, rather than *causes* it (see Naeye & Peters, 1980). The prevailing view certainly is that membranes rupture first, to be followed by amnionitis.

The preponderance of chorioamnionitis in very immature pregnancies (20–30 weeks) is striking (Lahra & Jeffery, 2004). It has often been linked to the less effective bacteriostatic nature of amnionic fluid in immature preg-

nancies (Anonymous, 1989a). Thadepalli et al. (1978) showed that amnionic fluid of the first trimester is least inhibitory against anaerobic organisms. Schlievert et al. (1975, 1976a,b, 1977) had similar results using various organisms for analysis. Their studies showed that the inhibitory moiety of the amnionic fluid contains a zinc-dependent special peptide that develops mostly after 20 weeks' gestation. Others had identified immunoglobulins in amnionic fluid (Galsk & Snyder, 1970) and that the fluid from patients with chorioamnionitis had elevated immunoglobulin levels (Blanco et al., 1983). Specific inhibition against *Mycoplasma* and *Chlamydia* was demonstrated in amnionic fluid by Thomas et al. (1988), and Gray et al. (1987) concluded that even the small quantities of type-specific streptococcal antibodies in amnionic fluid that they demonstrated may protect the fetus against this infection. All of these points may explain why chorioamnionitis is much more common during early pregnancy than toward term. It is our view that the more important aspect of labor initiation resides with inflammation of the decidua, and that the bacteriostatic activity of amnionic fluid is not the primary event preventing labor and chorioamnionitis during later gestation.

GENERAL CONSIDERATIONS OF CHORIOAMNIONITIS

The amnionic sac infection syndrome develops from infection that commences in the endocervix and vagina and then ascends (Fig. 20.23). Abundant evidence supports this opinion, and there is also much evidence that prematurity is often caused by such an ascending prenatal infection. Premature rupture of the membranes (PROM) often results and is then a common accompaniment of infection. Garite (1985) labeled it the "enigma of the obstetrician" because of the controversial aspects of diagnosis and management. A further problem is the difficulty in predicting rupture of membranes and premature delivery. It has been suggested that assessment of vaginal fibronectin may provide such a clue (Lockwood et al., 1991; Iams et al., 1995), but Feinberg and Kliman (1992), and others have taken exception to this approach. Gibbs and Blanco (1982) found that PROM complicates 4.5% to 7.6% of all deliveries, and that 1% of all gestations have preterm delivery with PROM. This study reviewed the evidence favoring the notion that PROM is often the consequence of subclinical vaginal infection. They also gave detailed protocols for management. McDuffie et al. (1992) showed in an experimental model that intracervical administration of coliform bacilli in rabbits leads to rapid and marked elevation of the various mediators that are usually associated with labor. Elst et al. (1991) found elevated prostaglandins and leukocytes in amniotic fluids aspirated by fetuses from spontaneous premature labor and concluded that chorioamnionitis may initiate preterm labor. Lettieri and her colleagues (1993) suggested that "idiopathic" preterm labor can be explained in 96%. They incriminated faulty implantation in one half of cases, infection in 38%, immunologic factors in 30%, cervical incompetence in 16%, uterine factors in 14%, maternal factors in 10%, trauma (surgery) in 8%, and fetal anomalies in 6%. It is our impression that ascending infection is the most important cause of preterm labor and PROM, certainly so in the 20- to 30-week gestation group. There are now numerous studies that support this contention. Romero et al. (1989e) examined the amnionic fluid aspirated from 264 women with preterm labor and with intact membranes. They found positive cultures in 91%; 42% delivered preterm neonates, 21.6% of which had positive amnionic fluid cultures. Preterm delivery was especially frequent when endotoxins were detected with the *Limulus* amebocyte lysate assay. The commonest organisms isolated were *Ureaplasma urealyticum, Fusobacterium* sp., and *Mycoplasma hominis*, but later studies have indicated a spectrum of other organisms (Romero et al., 1992a). Inflammatory lesions (chorioamnionitis, funisitis) are essentially present only when microbacterial contamination can be shown to exist in the amnionic cavity (Harger et al., 1991). This study also emphasized that antimicrobial therapy failed to prolong pregnancy when chorioamnionitis was extant.

There is now a very large body of investigations that incriminates all sorts of mediators in the initiation of labor during the process of ascending infection. Interleukin-1 was found elevated and championed by Taniguchi et al. (1991), but no elevation of levels of IL-1-receptor antagonists were identified (Romero et al., 1992b). In addition to IL-1, IL-6 was found to be increased in infections studied by Matsuzaki et al. (1991), but not in normal labor. Kelly et al. (1992) suggested that the "final common step of prostaglandin and antiprogestagen action in parturition was decidual release of IL-8." Hillier et al. (1992) found several cytokines and prostaglandin E_2 (PGE_2) to be elevated in amnionic fluid during preterm labor and suggested their usefulness in predicting labor. Tumor necrosis factor activates the cytokine machinery and may well be at the starting point of labor initiation by stimulating prostaglandin production from the decidua (Norwitz et al., 1992a,b; Romero et al., 1992c). Suffice it to say that the cytokine system is intimately involved in premature labor when it is caused by infection; absent inflammation, the kinin levels are not significantly elevated (Romero et al., 1993).

When membranes are ruptured and the endocervical mucus plug has disappeared, the amnionic cavity may be quickly colonized by organisms of the cervicovaginal tract (Miller et al., 1980a,b). Wahbeh et al. (1984) found that anaerobic organisms play an important role in PROM similar to the results of a study by Bobitt and Ledger (1977). When Pankuch et al. (1984) attempted the isolation of bacterial and chlamydial organisms from 75 placentas, they found that 72% of placentas with chorioamnionitis had bacteria (82% with clinical chorioamnionitis), whereas only 15% of uninflamed placentas contained organisms. Almost 50% were anaerobic organisms. When, as is frequently the case, no organisms are identified histologically by the pathologist one must consider that they are either histologically not recognized (e.g., mycoplasma, trichomonas, etc.) or that cytokines (chemokines: GRO-α and IL-8) may be the chemoattractants (Hsu et al., 1998). Johnson et al. (1981b) found in their large study of PROM that unless chorioamnionitis intervened, rapid delivery was not necessary. They cautioned that, with modern management, the risk to the fetus is primarily one of prematurity. Earlier studies of the same group had shown that neonatal infections were much more common in preterm than term infants, but that the risk of PROM alone was insignificant (Daikoku et al., 1981). Teppa and Roberts (2005) have now developed an enzymatic test for the apparently common asymptomatic bacteriuria in pregnancy but they do not correlate it with ascending infections. Many authors have suggested that maternal bacteriuria is specifically related to PROM and to prematurity (Naeye, 1979a), but it has not been confirmed by some well-controlled studies of maternal bacteriuria (Bryant et al., 1964). The relation of asymptomatic maternal bacteriuria to low birth weight and preterm delivery was reaffirmed by a meta-analysis of Romero et al. (1989d). They also believed that ascending infection was the mode for infection. An anamnestic lymphocyte response to the organism of maternal infection was demonstrated in some infants judged to be at high risk of dying (Wallach et al., 1969). Still somewhat controversial is whether ascending infection can truly be prevented by antibiotics and also whether treatment is beneficial (Christmas et al., 1992; Seo et al., 1992; Kirschbaum, 1993). Unresolved also is whether aggressive tocolysis is beneficial to prolonging the survival of neonates or prolong-

ing pregnancy significantly. Thorp et al. (2002) saw a mixed outcome pattern in their meta-analysis of 14 reports, and Combes et al. (2004) found no benefit from tocolysis in PPROM before 34 weeks in 130 cases studied, and reported significant maternal complications. Dinsmoor et al. (2004) found some prolongation of gestation with expectant management, but poor outcome nevertheless. Gibbs (2002) advocated that this is a topic for prevention rather than therapy, with which we agree. His experimental studies (Gibbs et al., 2002) clearly showed that, in rabbits, antibiotic therapy was unable to eradicate organisms from amnionic fluid or the fetus.

Another presumed cause of PROM, abortion, and premature delivery has been the syndrome of "incompetent cervix," thought to have a congenital origin (review by Borglin, 1962). It has been suggested that 0.1% to 1% of pregnancies are thus complicated, and that up to 20% of midtrimester abortions result from an incompetent cervix (Anonymous, 1977b). Gans et al. (1966) suggested that trauma is the most common antecedent of an incompetent cervix, a notion with which we agree, especially when prior surgery is considered. They reported favorable surgical repairs of the defect. The alleged etiology of trauma is well supported by a review of the topic (Anonymous, 1983a). Hagen and Skjeldestad (1993) studied the outcome of cervical laser conization with a case-control approach. They reported an increased frequency (38% vs. 6%) of premature births in the operated cases and recommended that conization be done only in high-grade in situ neoplasia. Barford and Rosen (1984) were more cautious in their assessment of diagnosis and therapy, and Charles and Edwards (1981) listed the many serious infectious complications (e.g., puerperal sepsis, chorioamnionitis) that may ensue, particularly when the Shirodkar stitch is undertaken during the second trimester of pregnancy. Heinemann et al. (1977) and others (e.g., Dunn et al., 1959) have reported maternal sepsis after intraamnionic *E. coli* infection in such cases. Abundant bacillary growth was present in placental capillaries, but there was only minimal inflammation in the case of Heinemann et al. (1977). Romero et al. (1992d) advocated that amniocentesis with culture should be undertaken before a cerclage is placed in the midtrimester; they found a high frequency of bacterial invasion. In our opinion, it is not likely that incompetent cervix is frequently an inherited defect; rather, we believe that trauma and infection are more probable antecedents. The cervix, affected by severe chronic cervicitis, is often patulous and prone to premature dilatation, which may be the origin of many of the 20% incompetent cervices cited to be associated with PROM. Leveno et al. (1986) published a study of gravid cervical dilatation that supported this assumption. They found that dilated cervices tend to lead to premature delivery; recurrent PROM and premature delivery are then serious problems. Gomez et al. (2005) also suggested that a foreshortened cervix is a risk factor for microbial ascending infection and derived this finding from a study of women in premature labor. This premature labor, however, is quite likely to have been the cause of labor in the first place that subsequently shortened the measured endocervical length. Asrat et al. (1991) studied 255 pregnancies in 121 patients and identified a recurrence rate of PROM in about one third. Interestingly, Salafia et al. (1991) found about the same frequency of the amnionic sac infection syndrome in premature births. An abnormally short cervix, as ascertained by vaginal ultrasonography, was also found to be associated with preterm delivery (Iams et al., 1996). Papiernik et al. (1998) reported that cervical shortening or dilatation of the cervix is a prerequisite for ascending infection and premature delivery, but only when vaginal infection exists. They opined that a reduction of preterm delivery can only be hoped for when prophylactic antibiotic therapy is practiced. Seaward et al. (1998) found that chorioamnionitis and maternal colonization with group B streptococci were the most important predictors of subsequent neonatal infection. Since that summary, numerous additional studies on cerclage or indomethacin treatment for the prevention of prematurity have been published. A meta-analysis by Belej-Rak (2003) showed that cerclage has no benefit for a sonographically identified short cervix, a finding subsequently confirmed by To et al. (2004). There are, however, different opinions on this very controversial and common dilemma faced by obstetricians. This is shown for instance by a series of papers that follow the one by Althuisius et al. (2000). Some authors find the Shirodkar operation to be a useful adjunct of therapy at the time of premature rupture of membranes, but others do not. Occasionally this treatment in the presence of active chorioamnionitis can have disastrous outcomes. This was shown in a set of twins of whom twin A died from *Actinomyces* sepsis after cerclage and treatment with various antibiotics; there was severe chorioamnionitis (Knee et al., 2004).

The presence of an intrauterine device (IUD) has been correlated with pelvic inflammatory disease (PID) in some studies (Lee et al., 1988). Other studies have been less convincing, and the large cooperative study published by Kessel (1989) asserted that the relation is mostly to the increased frequency of pelvic infections in general, noted since 1973, and not to IUD insertions. Generally, the device prevents pregnancy, but when it fails to do so (2% to 4%), premature labor and chorioamnionitis frequently ensue. The correlation of septic abortion and presence of an IUD has also been confirmed in the large study by Kessel (1989). In this context, Jewett (1973) reported a maternal death following *E. coli* infection at 22 weeks' gestation. Fatal maternal sepsis has also been reported as a complication of chorioamnionitis without an IUD (Webb, 1967). With cesarean section patients, myometritis is present in one third of asymptomatic patients whose inflamed membranes had ruptured for more than 6 hours (Azziz et al., 1988). An interesting association also exists between the occurrence of ectopic pregnancy and recurrent abortion (Fedele et al., 1989). It is likely that its basis is infection. Of parenthetical interest is the suggestion by Polunin (1958) that vaginal infection and birth practices in a North Bornean tribe (the Murut) caused sterility, and that it was the result of vaginal infection. In subsequent studies, an anaerobic coccal (probably streptococcal) infection was found to cause the vaginitis and PID found in this tribe (Hare & Polunin, 1960). Dinsmoor and Gibbs (1989) found that previous amnionic sac infection is not a risk factor for subsequent infection of the uterus.

Another topic of concern among the causes of premature labor, PROM, and fetal infections relates to the hypothesis that intercourse during late pregnancy may initiate premature delivery (Naeye, 1979b, 1980). Herbst (1979), in an editorial, reviewed evidence that meconium staining and risk of prematurity were greater when orgasm had been experienced during pregnancy. Naeye (1982) suggested that other causes of prematurity are smoking, parity, prior cervical surgery, and prior chorioamnionitis. There has been much criticism of these studies on coitus-related prematurity (e.g., Berg, 1980; Mills et al., 1981; Perkins, 1983), some of which has been answered by Naeye (1981, 1983, 1986). His finding of modal peaks of deliveries on certain days of presumed peak coital activity were used to further support a relation among coitus, infection, and premature labor. Klebanoff et al. (1984) could not accept this relation in their analysis of the same data, a study to which Naeye (1986) took exception. When Ekwo et al. (1993) studied coitus of late pregnancy to ascertain whether this bears risks for preterm rupture of membranes, they found that "most sexual positions and activities during late pregnancy are not associated with adverse outcomes." Neilson and Mutambira (1989) found no relationship of twin deliveries to coitus. Similarly, there was no relation to premature labor when frequent intercourse occurred in the patients studied by Read et al. (1993). This was so unless for some of those women who were already colonized with some specific organisms. Similarly, Kurki and Ylikorkala (1993) found that "in healthy nulliparous women, coitus during pregnancy is not related to bacterial vaginosis and does not predispose to preterm birth." The issue is currently not definitively decided, but additional data suggest that some relationship may exist between coitus and premature deliveries (Anonymous, 1984; Naeye, 1988a).

Specific Microorganisms

Neisseria gonorrhoeae is the organism responsible for gonorrhea, which occasionally complicates pregnancy. In a cervical culture study of 1309 antepartum patients, Kraus and Yen (1968) found a 5.73% asymptomatic infection rate during pregnancy, with 32% puerperal morbidity. They were then primarily concerned with ophthalmia neonatorum and did not address the possible risk posed by chorioamnionitis. This study and others indicated that active cervical infection with this organism does not necessarily lead to chorioamnionitis. Baddeley and Shardlow (1973) saw two patients with normal deliveries after gonococcal arthritis during pregnancy. Infection of the amnionic sac with gonococci has been reported by Nickerson (1973) and Rothbard et al. (1975). We have seen several cases as well, and they were similar to other types of acute chorioamnionitis. In Nickerson's case, the infection was not recognized until the gastric aspirate was cultured. The febrile patient was near term and had spontaneous rupture of membranes and a tender abdomen. The placenta was not studied.

Rothbard and colleagues (1975) probably reported the first case of antenatally diagnosed and treated gonorrheal chorioamnionitis. The aspirated amnionic fluid was purulent, and gram-negative diplococci (gonococci) were identified at 35 weeks' gestation. Cesarean section, performed after ampicillin therapy, led to the birth of a normal infant whose neonatal course was uneventful. The placenta was not described. Smith et al. (1989) reported a case of acute gonococcal chorioamnionitis with sepsis. Their patient had a dark red vaginal discharge at 32 weeks, emesis, chills, migratory arthralgia, and abdominal pain. The membranes were intact, and at amniocentesis, gonococci were demonstrated. The 1960-g infant did well. The placenta had acute chorioamnionitis.

Even acute gonococcal salpingitis has been described to complicate pregnancy (Genardy et al., 1976). Their patient was operated on for presumed appendicitis at 14 weeks' gestation; the fallopian tube had pus with gonococci identified therein, and the patient was successfully treated with cephalothin and kanamycin. At 37 weeks, she delivered a normal infant and a normal placenta. This event is rare, however, and when present, ascending infections involve the tube only early in gestation, before the decidua capsularis makes contact with the opposing uterine wall. We have seen only one placenta of a patient with a history of ruptured membranes for 4 weeks who, in addition to marked *E. coli* chorioamnionitis, had developed sepsis from acute unilateral salpingitis at 32 weeks' gestation. The inference in this patient was that the salpingitis developed after the chorioamnionitis, also by ascending means. Edwards and colleagues (1978) studied 178 patients with gonorrhea during pregnancy (2.75% of the pregnanies cared for), and reviewed the literature. They found chorioamnionitis in 26% (5% in controls). Premature rupture of membranes occurred significantly more often (63% versus 29%), a point that was denied by Amstey (1982).

Infections with **group B streptococci** (GBS) are important and frequent complications of the perinatal period, and we now differentiate between early- and late-onset neonatal infections because of their significant differences in outcome. This streptococcus is recognized to be one of the most virulent organisms during the perinatal period. Sepsis, pneumonia, and meningitis are common sequelae of this infection (Baker, 1977), and the organism emerged as the number two cause of neonatal meningitis (Anonymous, 1977a). Prematurity and premature rupture of membranes are strongly correlated with group B streptococcal infections. The diagnosis is often difficult unless it is actively pursued. Occult streptococcal infection is an important cause of fetal asphyxia, and stillbirths frequently occur with unruptured membranes (Naeye & Peters, 1978; Peevy & Chalhub, 1983). This important topic has been reviewed in some detail by Nizet and Rubens (2000) with special attention to the recently identified virulence factors. Pritzlaff et al. (2001) describe specific toxins of the streptococcal variants in a molecular publication and find a novel specific hemolysin and cytokinin and in yet another publication of these investigators (Doran et al., 2002a) the pathogenicity to the lung of various mutants is described. This organism has apparently specific toxicity to epithelial and also endothelial cells.

Novak and Platt (1985) described the placentas of 22 cases of early-onset group B streptococcal sepsis. They found that chorioamnionitis was present in 64%, 27% of patients had funisitis, and in 41% of these patients gram-positive organisms were found in the amnionic fluid. Importantly, though, some placentas showed no pathologic changes or had only villous edema. The authors were disappointed that, excepting neutropenia, the placental findings did not correlate well with fetal outcome. They also emphasized that the extensive colonization of amnion and the leukocytic response argued strongly against late acquisition of the organism by the fetus during fetal descent. They reviewed other studies that gave similar incidence figures and concluded that an important part of the fetal response is related to the specific enzymatic types of the individual organisms. In a study of autopsy files, de Paepe et al. (2004) found that GBS infection was diagnosed in 4.9% of neonatal autopsies (61 of 1236) and was the cause of death in 58 cases. Chorioamnionitis was found in 67% of preterm babies and only 33% of term infants. They concluded that "fetoplacental inflammation is a poor indicator of perinatal GBS infection." Importantly, when meconium is present, this apparently enhances the susceptibility of the neonate. Eidelman et al. (2002) found that meconium enhanced

growth of streptococci in amnionic fluid, whereas *E. coli* growth was inhibited.

Altshuler (1984) stated, "There is no inflammation in the placentas of at least 75 percent of newborns in whom group B β-hemolytic streptococcus has been cultured." Our experience also indicates that many placentas of streptococcus-infected babies, even those with neonatal sepsis, have no inflammation. Only very careful search for bacteria will identify the cocci on the amnion. Vigorita and Parmley (1979), on the other hand, described focal abscesses underneath the amnion, areas of epithelial necrosis, and found an accumulation of bacterial colonies in a relevant case. Although we have also seen such abscesses, we have wondered if double infection may have been the cause, as this observation differs so much from previous reports.

Group B streptococci may actively grow in amnionic fluid alone. Abbasi and colleagues (1987) showed that virulent strains of streptococci grew as well in amnionic fluid as in optimal bacterial culture media, although some differences were found among various strains. The authors believed that this point is clinically significant. But when the clinical manifestations of those patients in whom amnionic contamination was proved are compared with those without positive cultures, no differences of clinical risk factors were ascertained (Silver et al., 1990). The differentiation and designation of the many different streptococcal bacteria may not be widely appreciated. Table 20.1 summarizes their designation and features.

Numerous studies have addressed the need for early diagnosis and rapid therapy of perinatal group B streptococcal infection. The most modern studies employ a DNA probe for rapid detection (Yancey et al., 1993), in part because previous methods (enzyme-linked immunosorbent assay and Gram stain) were inefficient for screening tests (Hagay et al., 1993). Thus there is by no means agreement just how best to screen for the colonization, or how to deal with it when colonization is recognized. Gibbs and Blanco (1981) investigated 48 patients with bacteremia, 31 of which resulted from group B organisms. Endometritis and chorioamnionitis were the most commonly diagnosed clinical features. Although fever was often present, few localizing signs appeared. The authors also discussed effective therapy but some studies have shown that even intrapartum administration of antibiotics often does not prevent neonatal sepsis (Ascher et al., 1993). This has changed in the recent past following introduction of more rigorous protocols. Thus, Schrag et al. (2000) and Wendel et al. (2002) described practical and successful regimens of intrapartum therapy for high-risk patients. Andrews et al. (2000) discovered no organisms that were resistant to penicillin while finding resistance to erythromycin and clindamycin, and Gilson et al. (2000) advocated screening and intrapartum antibiotic therapy with good success. Towers and Briggs (2002) also described the marked decrease in frequency of early-onset disease when chemoprophylaxis is provided.

A prospective study of colonization with this organism was undertaken by Regan et al. (1981). They found a significant increase in PROM and an association with prematurity. That was not the case in the study reported by Amstey (1982), however. Singer and Campognone (1983) found organisms in the blood of immature stillborns associated with villous edema and mild chorioamnionitis. Two placentas showed acute and chronic villitis, which suggested to them a transplacental (hematogenous) infection. It may well have been a dual infection also. They emphasized the high risk of colonization, particularly during the second trimester of pregnancy. Matorras et al. (1989) showed that maternal colonization (rectal or vaginal) carried a significant risk for PROM. Cervical colonization was especially deleterious. Fetal death from streptococcal sepsis has even been described after intrauterine funipuncture for karyotyping (McColgin et al., 1989).

That this organism does not necessarily arrive in the fetus via hematogenous means, though, was shown by M.A. Pass et al. (1980). They found a severely colonized dichorionic twin A whose co-twin (B) did not have the infection. They believed that twin pregnancies are particularly vulnerable. Doran et al. (2002b), however, described a set of monozygotic (MZ) twins with late-onset disease causing fulminant fatal meningitis in twin A, while twin B recovered completely. The twins had a monochorionic placenta but it was not further described. Forsnes et al. (1998a) described hydrops in one diamnionic/monochorionic (DiMo) twin from whose amnionic

Table 20.1. Classification of aerobic streptococci

Group	Designation of species	Blood agar reaction[a]
A	*S. pyogenes*	β-hemolytic
B	*S. agalactiae*	Usually β-hemolytic
C[b]	Several species	β-hemolytic
D (enterococci)	*S. faecalis*, *S. faecium*	α-, β- or nonhemolytic
E (nonenterococci)	*S. bovis*	α-, or nonhemolytic
F	*S. anginosus*	Small colony β[c]
G[b]	Many species	Usually β-hemolytic[c]
Viridans hemolytic species		α-hemolytic
Pneumococci	*S. pneumoniae*	α-hemolytic

[a] β reaction is clear, complete hemolysis; α reaction is green discoloration, partial hemolysis.
[b] Groups C and G, β-hemolytic streptococci.
[c] The British classify minute colonies of groups C, F, and G β-hemolytic streptococci and Lancefield-groupable, and capnophilic strains of α- and nonhemolytic *S. intermedius* and *S. constellatus* as *S. milleri*. The Centers for Disease Control uses the designation *S. anginosus* for minute colonies of β-streptococci and retains the designations *S. intermedius* and *S. constellatus* (C. Davies, personal communication, 1989).
Source: Modified from Gibbs & Blanco (1981).

fluid adenovirus was grown. Both twins died at 26 weeks and their cardiac size did not indicate the presence of twin transfusion syndrome. It was assumed that transplacental infection took place in only one twin. Anastomoses were not described. Iams and O'Shaughnessy (1982), who evaluated antenatal versus intrapartum screening, found no advantage in the former method, whereas Pass et al. (1982) correlated infection with puerperal fever and the finding of frequent chorioamnionitis in cases of perinatal infection. The attack rate in their study was two in 1000 deliveries. They recommended intrapartum antibiotic prophylaxis, as did Boyer and Gotoff (1986). Strickland et al. (1990) also suggested a frequency of two early-onset infections in 1000 births and found intrapartum screening for this infection to be cost-effective because of the severe handicaps that can result. Thomsen and colleagues (1987) found that urinary group B streptococcal infection correlated with preterm labor, and they also reported a beneficial effect from penicillin therapy. Dykes et al. (1985) investigated women who gave birth to infected babies. Chronic carriage in the urinary tract, without immunologic response, was therein apparent. Similar findings were reported by Moller et al. (1984). They also found an increased risk of ruptured membranes. Matorras et al. (1989) found that PROM was significantly correlated with vaginal or rectal carrier status. It has also been shown that successive group B streptococcal infection, with early-onset disease of neonates, can occur despite proper antibiotic therapy (Carstensen et al., 1988).

For all these reasons, rapid diagnosis of infection with group B streptococci is urgent, a point addressed in several studies (e.g., Morales et al., 1986; Morales & Lim, 1987). Morales et al. used coagglutination methods for identification; Sandy et al. (1988) tested Gram stains of cervicovaginal swabs; they found it to be an unreliable means for diagnosis. Of alternative methods explored in an editorial, most were considered to be unsatisfactory for routine use (Anonymous, 1986). Latex agglutination tests from swabs may be a useful means of rapid identification (Howe et al., 1987; Stiller et al., 1989). Baker et al. (1988) obtained promising results from immunization of pregnant women. In a large review of the possibility for immunization, Coleman et al. (1992) suggested that such vaccination is attainable and that studies in that direction be pursued; antigens such as cell wall polysaccharides and protein C are the most promising to be investigated.

The effect of this infection can be devastating to the newborn (and fetus), and its onset may be rapid. The neonatal diagnosis, manifestations, and therapy were lucidly discussed by McCracken (1976). Contrary to one's hopes, immediate penicillin therapy to the immature neonate does not prevent early-onset disease, nor does it reduce the excessive mortality (Pyati et al., 1983).

Of interest to the pathologist is the study of Katzenstein et al. (1976). Dissatisfied with the frequency of autopsy diagnosis of hyaline membrane disease in pregnancies at risk, they used immunofluorescence (on formalin-fixed tissue) to reexamine eight appropriate cases. They identified streptococci in the pulmonary hyaline membranes of five neonatal deaths. These structures were so numerous in one case that they appeared to make up the bulk of the fibrinous membrane. The deaths had previously been attributed to routine hyaline membrane disease at routine autopsy.

Hyde et al. (1989) have shown experimentally that extracts from cultures of this organism may cause isolated portions of umbilical vein wall to contract severely. They suggested that such effects may occur in vivo during intraamnionic infections, and that it may lead to reduced venous return from the placenta, causing fetal damage. Clinical investigations of this phenomenon are now commencing. Fleming et al. (1991) found a correlation of S/D (systolic/diastolic) ratios and biophysical profiles with chorioamnionitis, whereas Leo et al. (1992) did not. It must be pointed out, however, that the latter group did not study the placentas, and other problems exist with the protocol. It is too early to make decisions as to the possible value of predicting chorioamnionitis/funisitis with this methodology.

Group A β-hemolytic streptococci pose serious problems for mother and fetus (Swingler et al., 1988). Antenatal acquisition was shown by Monif (1975) in a febrile patient with a tender uterus at 34 weeks' gestation. The membranes were unruptured, and the cervix was closed. A depressed infant was born with leukocytosis, left shift of white blood cells, and positive cord blood culture. Placental histologic study was not undertaken. Other cases were reviewed by Lehtonen et al. (1984). The infection responds readily to penicillin or ampicillin, and the umbilical stump may be a reservoir for the organism. Puerperal infection with this organism, however, may pose serious risks (Silver et al., 1992). Both of their seriously ill patients required hysterectomy, but their pregnancies had ended uneventfully.

Fatal maternal and fetal infection with *Streptococcus pneumoniae* (type III) was reported by Tarpay et al. (1980); that placenta also was not studied. Duff and Gibbs (1983) identified two similar infections with *S. pneumoniae* demonstrable in amnionic fluid. They thought that ascending infection was unlikely because of the stringent pH requirements (pH 6.5 to 8.3) of the organism. They did not identify the source of infection and did not report on the placenta. Andreu et al. (1989), however, reported chorioamnionitis in the placentas of several infants, prenatally infected with this organism and having pneumonia.

Haemophilus influenzae was contracted prenatally in a premature infant reported by Barton et al. (1982). It had septicemia and recovered after ampicillin therapy. The membranes had ruptured 15 hours before delivery.

The placenta was not described. Gibson and Williams (1978) observed this infection in a 28-week gestation complicated by leukorrhea, abdominal pain, and fever. The amnionic fluid was opaque and contained the organisms on smears. The placenta had chorioamnionitis and funisitis. The infant died from hyaline membrane disease. There was no pneumonia. A study by Campognone and Singer (1986) of 19 patients with this infection drew attention to the serious nature of this disease. All of their cases had chorioamnionitis, and three had acute villitis in addition. Winn and Egley (1987) added another case with chorioamnionitis and funisitis. The patient had intact membranes. The organisms may be readily identified as gram-negative rods in smears. Rusan and her colleagues (1991) agree that this infection poses serious problems; they undertook a retrospective review and found 13 cases with chorioamnionitis or endometritis over a 10-year span. Of 23 infected neonates, 15 presented with sepsis or pneumonia.

Diplococcus pneumoniae (*Streptococcus pneumoniae*) was the cause of neonatal laryngitis in a term infant delivered to a febrile patient with positive amnion and cervical cultures (Hazard et al., 1964). It may here be mentioned that smears of the placental surface have been usefully employed by Nessmann-Emmanuelli et al. (1983) in establishing prenatal infection. Positive smears were obtained in 9% of a high-risk group (63% gram-positive, 17% gram-negative, and 20% mixed). It was especially useful for group B streptococcal and *E. coli* infections.

Gram-negative bacilli, in particular *E. coli*, frequently cause chorioamnionitis. Their association with neonatal meningitis is well known (Kagan et al., 1949; Watson, 1957; McCracken & Sarff, 1974). That this organism, especially the K1 type, is transmitted vertically has been firmly established by the large cooperative study of Sarff et al. (1975). These authors found a strong association with maternal rectal colonization of the organism and likened the acquisition to that of streptococcal infection. The investigators did not examine placentas. Their concept of pathogenesis included lung infection, intestinal infection, sepsis, and meningitis. We believe that the modus of transmission for neonatal meningitis is often through the aspirated amnionic fluid via the middle ear. DeSa (1974) has shown that squames, admixed with pus and organisms, are often found in the middle ears of stillborns and neonatal deaths.

Salmonella typhi and other salmonella organisms may cause meningitis of neonates. They may be transmitted vaginally. Pugh and Vakil (1952), Watson (1958), and Scialli and Rarick (1992) reported cases of congenital infection and some fetal deaths, and they also reviewed the literature. Infection by symptomatic women or carriers was also shown by Luder and Tomson (1963), and Freedman et al. (1970). The placenta is usually not mentioned. An exception is the case reported by Awadalla et al. (1985) of a patient with gastroenteritis at 26 weeks' gestation. A foul-smelling intact gestational sac containing cloudy amnionic fluid was delivered. Blood, stool, cervical specimens, and amnionic fluid yielded the organism. Despite these findings, the authors were of the opinion that transplacental, rather than ascending, infection took place. When Roll et al. (1996) saw a premature neonate die with *Salmonella enteritidis* infection, they cultured the organism from the infant and placenta, but there was no evidence of chorioamnionitis. Seoud et al. (1988) recorded the occurrence of typhoid fever during pregnancy in 13 patients. One infant died with pneumonia. The mothers were treated with chloramphenicol and did well.

Infection with *Shigella sonnei* caused septicemia and enterocolitis in a term infant reported by Kraybill and Controni (1968). Prenatal infection of this infant seemed likely, but the placenta was not studied.

Clostridium perfringens infection occasionally complicates pregnancy. Among anaerobic infections, this type has been particularly feared because of the postabortal sepsis and uterine gas gangrene that may be life-threatening for the gravida (Ramsey, 1949). Nash et al. (1963) described a patient at 35 weeks' gestation whose membranes had ruptured for 5 days, a tender uterus, fetal death, and abdominal crepitation from gas infiltration. They carefully described the placenta: It had a greenish amnionic surface and a putrefactive odor. The purulent exudate covered the membranes and fetal placental surface; it contained gram-positive rods. The maternal surface and villous tissue were not involved. A similar case is shown in Figure 20.25. Several reports of abortion due to *C. perfringens* infection have been published that emphasized the severity of this infection and the frequent lethal outcome (Decker & Hall, 1966; Pritchard & Whalley, 1971). Decker and Hall (1966) demonstrated that inflammatory exudate and necrosis of villous tissue may be found in septic cases, and the fetus may be invaded by organisms.

Diphtheroids or corynebacteria are frequent normal vaginal inhabitants and can often be cultured from placental surfaces. They have occasionally been shown to cause chorioamnionitis. Fitter et al. (1979) described a case of funisitis and chorioamnionitis due to *Corynebacterium kutscheri*. It occurred at 26 weeks of pregnancy in a grand multipara who delivered 24 hours after rupture of membranes. Gram-positive organisms were demonstrated and were grown in pure culture from cord, membranes, rectum, nose, throat, eye, and external ear. There was no sepsis in the 980-g premature infant who survived after ampicillin and gentamicin therapy. The placental surface was discolored and had gray-brown plaques. Similar plaques were present on the umbilical cord. The plaques were composed of organisms that also invaded the underlying tissue. Funisitis and chorioamnio-

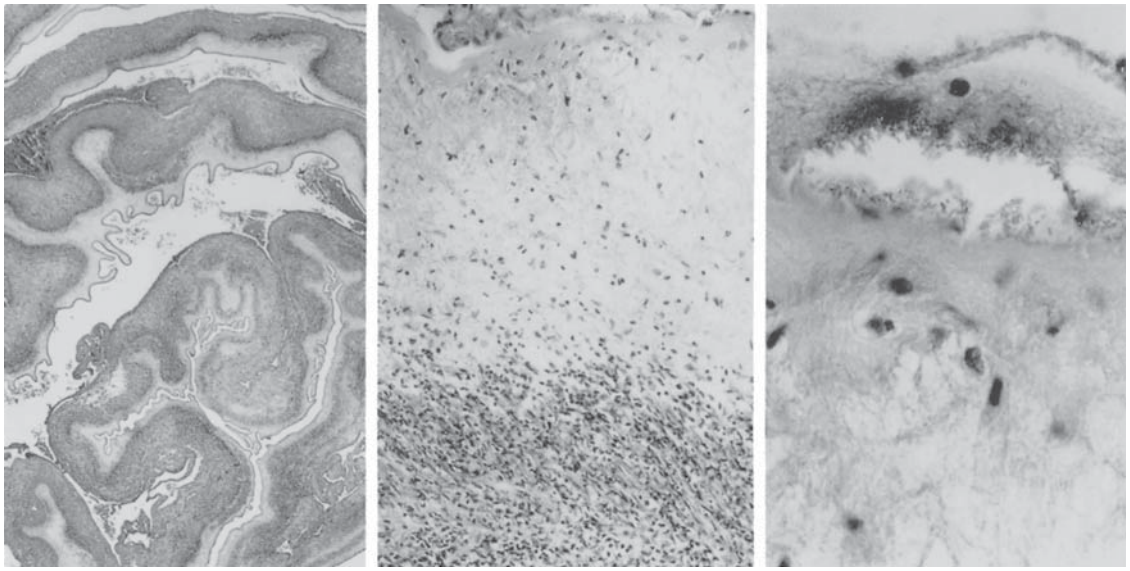

FIGURE 20.25. Clostridial chorioamnionitis at term. The membranes were friable and meconium-stained. The infant survived with antibiotic therapy. Membrane roll (left) shows intensive deciduitis and chorionitis. Note the umbilical arteritis (center, right) with a pocket of gram-positive rods underneath the amnion. Touch preparations were strongly positive. H&E ×16 (left); ×160 (center); ×640 (right).

nitis were pronounced. The case proves that not all diphtheroids isolated from the placenta or amnionic fluid are due to vaginal contamination at delivery. In this case, the infection must have occurred prior to membrane rupture.

Altshuler and Hyde (1985, 1988) have drawn attention to the importance of *Fusobacterium necrophorum* and *F. nucleatum* infections as significant complications of pregnancy. These pleomorphic, filamentous, gram-negative, anaerobic organisms were isolated from three of 297 placentas examined for various indications. These authors described in detail the fluorescent antibody identification, chromatography, and usefulness of the Warthin-Starry stain for identification on slides. Brown-Brenn stains were not so useful for demonstrating the bacteria, and in hematoxylin and eosin (H&E) preparations the organisms were even more difficult to identify microscopically. It is also important to note that Bouin's fixative makes their demonstration particularly difficult. Of 92 prematurely delivered placentas, 62 had chorioamnionitis, and of the latter, 11 (18%) had filamentous organisms in the membranes.

In the rat animal model developed by Altshuler and Hyde (1985), inflammation similar to chorioamnionitis was consistently produced. In a subsequent contribution (Altshuler & Hyde, 1988), these investigators reaffirmed the association of fusobacterial infection and prematurity. Among 586 placentas examined, they identified 14 with fusobacteria, and from their literature review, it is evident that as many as 30% of patients with occult chorioamnionitis may be infected with a *Fusobacterium* species. A typical case of fusobacterial chorioamnionitis is shown in Figure 20.26. It was associated with the scattered villous edema (Fig. 20.27) that Naeye et al. (1983) considered to be so important in causing prenatal hypoxia in association with chorioamnionitis and prematurity. Easterling and Garite (1985) reported three cases of fusobacterial infection and emphasized the importance of this rarely recognized organism as a cause of premature labor, and Romero et al. (1989e) found it commonly in prenatally obtained amnionic fluid with intact membranes. Cox et al. (1988) found bacterial endotoxin in the amnionic fluid of a patient with fusobacterial infection of a preterm delivery, reaffirming the suggestion by Altshuler and Hyde (1988) that these organisms are rich in lipopolysaccharide.

Bacteroides fragilis was found to be the cause of ascending infection in five of 15 patients with premature rupture of membranes reported by Evaldson et al. (1982). *Campylobacter (Vibrio) fetus*, a common enteric pathogen in humans and a common cause of venereally transmitted abortion in hoofstock, has been described to cause placentitis, infarcts, and fetal death (Gribble et al., 1981). Their patient had fever for 3 weeks and fetal death at 19 weeks. The amnionic fluid and placental surface were normal, but histologically there were areas of villous necrosis and "acute inflammation in the villous tissue." The organism was isolated from maternal blood, placenta and fetal spleen. These authors reviewed the few other cases reported with pregnancy; when described, the placentas were similar to their case. The route or source of infection was not identified in any of the cases, nor was

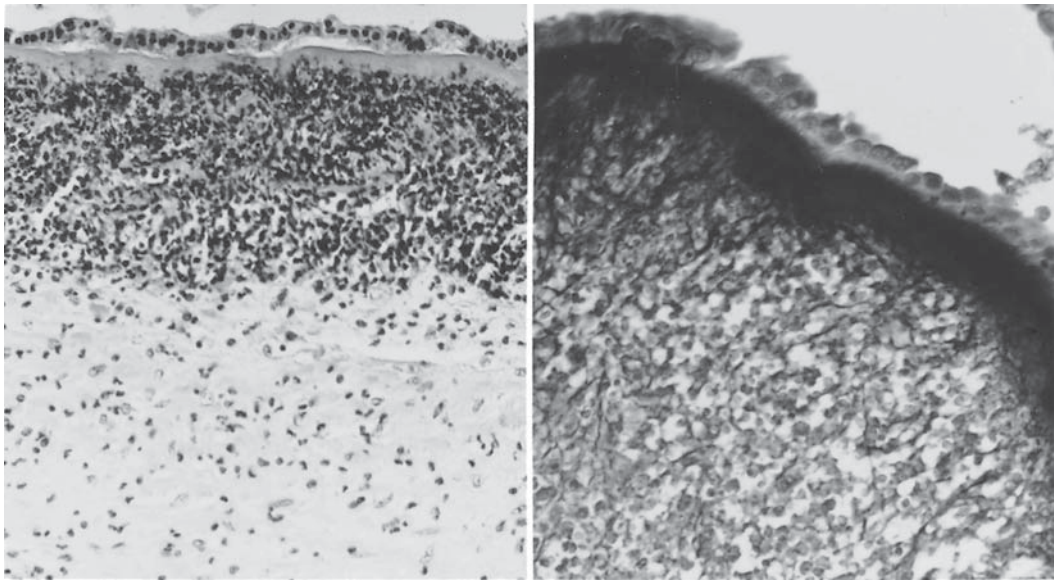

FIGURE 20.26. Chorioamnionitis due to fusobacteria in the placenta at 23 weeks' gestation. The placental surface was opaque. Fusobacteria were also found in the fetal lung. At left are Bouin-fixed membranes with inflammation; few indications exist of the massive bacterial growth seen with the silver stain at right. The dark filaments radiating from the amnionic basement membrane are easily identified as the filamentous organisms. H&E ×160 (left); GMS, ×240 (right).

venereal transmission verified. In the case described by Meyer et al. (1997), maternal colitis complicated a 22-week pregnancy, resulting in maternal sepsis, acute villitis, and fetal demise. The organism was identified genetically as well as by Warthin-Starry stain and occurred primarily within the immature villi. Some patients had recurrent abortions. Placental tropism has been suggested to exist in sheep. The earlier literature of infection with this organism was reviewed by White (1967).

Chorioamnionitis due to *Streptobacillus moniliformis*, the cause of rat-bite fever, was reported by Faro et al. (1980). The patient had cervical cerclage for repeated abortions, and with unruptured membranes, amniocentesis yielded pus and gram-negative rods. The placenta had a fetid odor. The patient's house was infested with rats. The organism also causes the Haverhill (milk) fever.

Gibbs et al. (1987) isolated the gram-variable organism *Gardnerella (Hemophilus, Corynebacterium) vaginalis* from 28% of 86 patients who had intraamnionic infection. Because controls had a similar frequency of isolation (21%), the authors suggested that this common vaginal organism is part of a microbial spectrum that does not cause PROM. We have isolated it occasionally from maternal and neonatal blood; it causes mild disease, but severe chorioamnionitis, premature delivery, and demise were reported by Pinar et al. (1998). Their description is

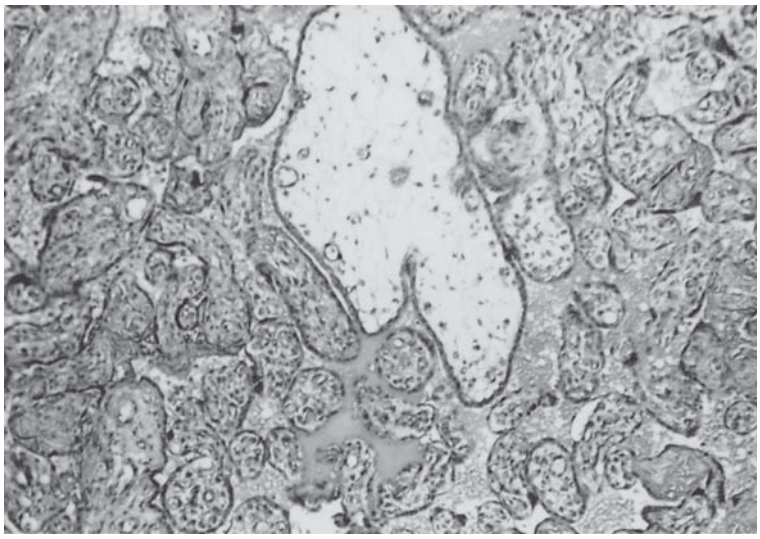

FIGURE 20.27. Villi of placenta in Figure 20.26, showing scattered villous edema. H&E ×160.

of further interest in that it depicted the turquoise staining of the umbilical cord secondary to amnionic injection of indigo carmine. Hillier et al. (1988), in a case-control study of chorioamnionitis, isolated *G. vaginalis* in 26% and *Ureaplasma urealyticum* in 47% of cases of prematurely delivered infants. They suggested that these organisms are etiologically important.

Tularemia is an uncommon disease, but the responsible organism (*Francisella tularensis*) had once been described as infecting placenta and fetus (Lide, 1947). The placenta of the macerated fetus showed granulomatous lesions with frequent central necrosis, and similar granulomas were found in the fetus. The patient had become infected while preparing rabbits for eating.

Brucellosis is caused by a variety of organisms belonging to the genus *Brucella*. Malta and Bang fevers, in humans, are due to infection with these organisms, but a wide variety of animal diseases are frequently caused by host-specific species of these organisms (Moore & Schnurrenberger, 1981). Among the animal diseases, abortion and placentitis are prominent findings. The placental lesions are frequently characteristic (Molello et al., 1963) and have been experimentally studied in goat by Anderson and his colleagues (1986a,b). Human infection with several of the *Brucella* species has been well documented. The infection may be fatal or lead to protracted disease; often it is self-limited, and the organism appears to be acquired from contact with animals or their products, especially raw milk and unpasteurized cheese (Anonymous, 1983b). Although human abortions have been described as being due to *Brucella abortus*, and the organism has been isolated from the fetus (Carpenter & Boak, 1931), it is an uncommon event. In cattle, the organisms are much enriched in placental cotyledons and allantoic fluid, and in mice this infection has provided an important model (Tobias et al., 1993). Meador and Deyoe (1989) depicted large numbers of these bacteria in the trophoblast of infected bovine placentas. Sarram et al. (1974) isolated *Brucella melitensis* from the placenta of abortion in a highly endemic area, and they suggested a causal relation to the abortion. The placentas were not described. The topic was completely reviewed by Porreco and Haverkamp (1974). They found little evidence of an increased abortion rate with this infection and cited only a few cases with positive isolation from the placenta or fetus. The patient they described had verified infection from fresh goat cheese during the 32nd week of gestation. She was treated with kanamycin and delivered a healthy infant at term. The placenta was normal. No characteristic lesions have been described in the human placenta with this disease. Salpingitis has often been reported with brucellosis, and sexual transmission was suggested in several studies (see Ruben et al., 1991). Mofleh et al. (1996) stated that, in endemic regions, infection commonly occurs from animals and their placentas.

Leprosy

Leprosy is due to *Mycobacterium leprae*. It is now relatively uncommon in the United States, but pregnancy-complicating leprosy has been investigated on many occasions. It has been reported that vertical transmission either usually is uncommon or does not occur, although Duncan et al. (1983) described two young children (12 and 17 months of age) with leprosy. Whether these children acquired the disease transplacentally or shortly after birth remains unknown. The authors examined sections of the placenta and failed to identify acid-fast bacilli. When they made concentrates of the 10 most "bacilliferous" patients' placentas, they found only scanty organisms or cell debris.

Maurus (1978) found no organisms in one placenta and gave up searching for organisms in the placenta following a report by King and Marks (1958) that said they were unable to identify placental organisms in treated leprosy. This statement contrasts with earlier reports, summarized by Duncan (1985), in which frequent abortion with bacterial isolation of organisms from placenta and cord blood was alleged.

For this reason, the detailed study of the human placenta in leprosy by Duncan et al. (1984) is of great value. In their review of the literature, there was one reported placenta with a granulomatous lepromatous lesion in villi; *M. leprae* was present in 66 of 172 placentas studied in the past. Duncan and colleagues (1984) reported a detailed investigation of 81 placentas from leprous women. No lepromatous lesions were detected histologically in the placentas by electron microscopy or immunologic study. Homogenates of placentas from two patients with active lepromatous leprosy yielded a few acid-fast bacilli. The previously recognized relatively small size of placentas in leprosy (Duncan, 1980) was reaffirmed. This "hypoplasia," however, was now held to be due to smaller placental cell sizes (rather than cell numbers) and not to an altered immune status. Patients with leprosy have depressed T-cell reactivity that is allegedly worse during pregnancy. For unknown reasons, these mothers excrete reduced amounts of estriol during pregnancy (Duncan & Oakey, 1982).

Nine-banded armadillos suffer leprosy frequently, and they can be infected with the human organism. When Job et al. (1987) studied the placentas of three pregnant nine-banded armadillos, they found acid-fast organisms in decidua, trophoblast, and villous cores, as well as in the spleens of some fetuses. Although focal villous necrosis was found, no granulomas were seen in the placentas. One animal had thrombosed cord vessels. In light of the occasional finding of organisms in placentas from leprous women, and because of some degree of similarity between armadillo and human placentas, vertical transmission remains a possibility, even though it may be uncommon.

Tuberculosis

In contrast to leprosy, congenital tuberculosis has been repeatedly demonstrated to occur, despite the fact that generalized tuberculosis is a frequent cause of sterility. In some cases there is doubt as to the timing of infection. Neonatal disease may have been acquired postpartum from milk or sputum of an infected mother. No epidemiologic doubt, however, exists about the disease in the macerated stillborn with the extrauterine pregnancy described by Nokes et al. (1957). This 23-cm crown–rump (CR) fetus, removed from an abdominal implantation, had multiple caseating pulmonary nodules and acid-fast bacilli in the liver, spleen, and kidneys. The placenta had many hard, white plaques that represented tubercles that contained acid-fast organisms. The patient had a partially tubally implanted pregnancy with tuberculous salpingitis, and miliary tuberculosis existed in most organs. The authors reviewed briefly 68 previously reported cases of extrauterine pregnancies complicated by tuberculosis.

Beitzke (1935) established criteria for the acceptance of congenital tuberculosis, which is now a rare and preventable disease of infants. These criteria included evidence of hematogenous infection via the umbilical vein. Beitzke also emphasized the need of separating the infant from the mother at birth. Nemir and O'Hare (1985) reviewed diagnostic criteria, reported the longest follow-up of a severely infected child, and gathered more than 200 cases from the literature. Their own case was criticized by Corrall (1986) as not fulfilling all of the established criteria. The discussion further elaborated on the difficulties of distinguishing truly transplacentally acquired tuberculosis from infection transmitted by inhalation of infected amnionic fluid and from neonatal disease acquired nosocomially.

The placenta has rarely been examined in putative cases of congenital tuberculosis. Schmorl and Kockel (1894) examined three patients who died with tuberculosis during pregnancy. The placentas appeared grossly normal. The fetuses were near term; all three associated placentas contained typical but rare granulomas with giant cells in the villous tissue. In two fetuses, tuberculous lesions were also found; the placental membranes were uniformly negative. Schmorl and Geipel (1904) found nine additional cases of placental tuberculosis among 20 new specimens. For some of these specimens, more than 2000 sections had to be prepared before tubercles were found. The authors insisted that acid-fast stains must be made, lest early lesions be overlooked. Even so, identification of acid-fast organisms required a prolonged search. Bacilli were frequently found in fetal vessels, intervillous fibrin, and septa. Warthin (1907) provided additional detailed descriptions of placental tuberculosis, with numerous tubercles and acid-fast bacilli identified. He found that the decidua contained areas of necrosis but no giant cells; there were many intervillous and villous granulomas, and the chorion was involved only sparsely. In a previous case, he also made thousands of sections to verify tuberculous infection. His initial opinion that the syncytium was resistant to infection was subsequently modified because he saw necrosis of trophoblast.

Boesaart (1959) also found tubercles in the placenta of an infected patient whose infant remained well. We saw a placenta membranacea at 35 weeks' gestation from a patient with tuberculous peritonitis. The placental floor had several tuberculous granulomas. The neonate was well and was treated prophylactically (Kaplan et al., 1980). In the same report we demonstrated numerous acid-fast bacilli in the therapeutically aborted villous tissue of a patient who had cavitary tuberculosis for which she was taking appropriate medication. There were neither necrosis nor a granulomatous reaction in this endometrium. Finding the organisms was unexpected. In other cases we have identified acute granulomas (consisting mostly of neutrophils) adjacent to villi and destroying the trophoblast and isolated giant cells in stem villi but without inflammation. We have also been impressed with the extensive and unusual necrosis at the decidua basalis and capsularis in patients with disseminated tuberculosis during pregnancy. The areas appeared bright yellow macroscopically and had a "cheesy" complexion microscopically, similar to what one expects in large granulomas.

Listeriosis

Listeriosis is caused by a gram-positive bacillus that is occasionally confused with diphtheroids. The disease occurs in a wide variety of mammals and birds, as well as in humans (Dennis, 1968). The literature suggests that the human disease is underdiagnosed (Bowmer et al., 1973). Most adults successfully eliminate the causative organism *Listeria monocytogenes*. Immunodeficiency of adults (Nieman & Lorber, 1980; Wetli et al., 1983), various chronic disease states (Boucher et al., 1984), and characteristically pregnancy may be complicated by significant disease (Gantz et al., 1975). Transmission from mother's milk has been recorded in neonates (Svabic-Vlahovic et al., 1988). Nosocomial infection occurs in nurseries (Nelson et al., 1985), and direct contact with infected animals has also caused infection (Anonymous, 1980). Southwick and Purich (1996) have reviewed the complex microbiology with this organism. Several serologic subtypes exist and specific antibodies are useful for diagnosis in otherwise difficult cases (Roberts, 1997).

Food-borne acquisition of the organism is the most common mode of infection (Gill, 1988; Lamont et al., 1988; Jones, 1990). Numerous epidemics have been reported, and the source of bacteria has been defined in some (Anonymous, 1985). Some of these epidemics have originated from pasteurized milk (D.W. Fleming et al.,

1985), Mexican-style cheese (Linnan et al., 1988), cabbage contaminated by sheep feces and made into coleslaw (Schlech et al., 1983), poorly cooked sausage and chicken (Schwartz et al., 1988), pâté (37 of 73 examined contained the organisms; Morris & Ribeiro, 1989), and other sources. At times, the precise source of an infection could not be defined, despite intensive search (Filice et al., 1978), but a gastrointestinal route appears to be the most likely mode of infection (Breer & Schopfer, 1988). The organism may survive moderate heat, and it thrives in chilled food (Kerr et al., 1988; Gilbert et al., 1989). Guidelines have thus been established for the food industry in order to avoid wide dissemination of this ubiquitous agent to susceptible people (Update, 1988).

The implication that livestock is the cause of transmission of this infection has been challenged, as the organism also occurs in the stool of many normal people and in the soil (Low & Donachie, 1989). Ortel (1975) investigated stools from a large population of normal people after a devastating outbreak occurred in Halle during 1968. Pregnant patients had a 24% rate of contamination (6.5% after delivery), meatpackers 3.6%, and nurse-midwives 9%; finally, the personnel of a laboratory had a 91.6% (!) rate of carriage.

The organism is a danger principally to pregnant women, newborns, and immunocompromised individuals. A 60% perinatal mortality has been ascribed to this infection (Barresi, 1980). We have seen congenital listeriosis in the offspring of a microbiology laboratory technician, suggesting that special vigilance is needed when such personnel are pregnant. Fortunately, the neonate was promptly treated and survived. In infants, listeriosis is known as granulomatosis infantiseptica. "Granulomatosis" is a misnomer because the visible lesions are truly abscesses, not granulomas (Seeliger, 1955). An autopsy report of seven children with perinatal listeriosis indicated that grossly visible microabscesses are relatively uncommon (Klatt et al., 1986). During an outbreak in Los Angeles, which originated from infected cheese, maternal pyrexia and a high index of suspicion were the most essential factors for the early diagnosis (Boucher & Yonekura, 1986). Neonatal meningitis is a serious complication of fetal infection with this organism (Ahlfors et al., 1977; Visintine et al., 1977; Laugier et al., 1978). A rash is often present in the neonate, and gastric aspirates as well as Gram stains (and culture) of skin rashes are helpful for identifying the organism (Halliday & Hirata, 1979). One case of nonimmune fetal hydrops has been attributed to listeriosis; the placenta and stillborn fetus had numerous abscesses (Gembruch et al., 1987). The diagnosis is easily established from cultures, when the infection is suspected. Berche et al. (1990) found that anti-listeriolysin O titers quickly develop after infection, and that they are useful for diagnosis. Despite the infrequency of listeriosis in Saudi Arabia, Boukhari et al. (1999) described a term neonate with meningitis who was successfully treated, the first case in that country with early-onset disease. Benshushan et al. (2002) reviewed charts of neonates from a 10-year time span in Israel and found 11 pregnant patients with listeriosis in mother and infant. In the five placental examinations available, all had chorioamnionitis and abscesses. Plaza and Gilbert-Barness (2001) described a stillborn intrauterine growth restriction (IUGR) infant with listeriosis and superbly illustrated the placental lesions.

The placenta in listeriosis has the following characteristic lesions: villous abscesses, villous necrosis, necrotizing villitis, and an abundance of bacterial growth on the amnionic surface, usually accompanied by chorioamnionitis. Case reports with good descriptions of these lesions have been provided by Olding and Philipson (1960), Driscoll et al. (1962), Soma (1979), Roberts (1997) and many other pathologists. Yamazaki et al. (1977) found abscesses, chorioamnionitis, and funisitis in a stillborn with proved granulomatosis infantiseptica, but they were unable to demonstrate the organisms in the placenta. They referred to other authors with a similar experience. The development of unusual macroabscesses in congenital listeriosis was described by Steele and Jacobs (1979), and Topalovski et al. (1993) thought that the diagnosis could be made solely from a placental examination. They depicted the macroabscesses in the placenta and suggested that silver impregnation is a better means to demonstrate the organisms than a Gram stain. The diagnosis of listeriosis complicating pregnancy is important because prompt therapy with ampicillin rapidly cures the maternal and fetal infections. There is also good evidence that listeriosis is a common cause of abortion in France (Lallemand et al., 1992), and produces similar pathologic lesions. Forsnes et al. (1998b) observed an interesting diamnionic/dichorionic twin pregnancy in which the "higher" twin B had died in utero from listeriosis (culture proven), with twin A remaining healthy and delivered at 34 weeks. Areas of avascular villi and chorioamnionitis were found in the placenta of twin B. Another dichorionic twin gestation with congenital listeriosis comes from Beinder et al. (1999). Here, again, twin A was healthy but twin B died from the disease.

Aside from the usually opaque surface of the placenta, which is occasionally described as greenish, there are often typical abscesses visible in cross sections of the fresh placenta (Figs. 20.28 and 20.29). When smears of these yellowish lesions are stained with Gram solution, the organisms are often readily apparent. Microscopically, the abscess frequently has a central area of necrosis and is composed of a massive PMNL infiltration (Fig. 20.30). The chorioamnionitis is usually severe and often extends into the villous tissue; the amnion commonly contains a large number of organisms. There is no doubt that some of them have proliferated during cold storage

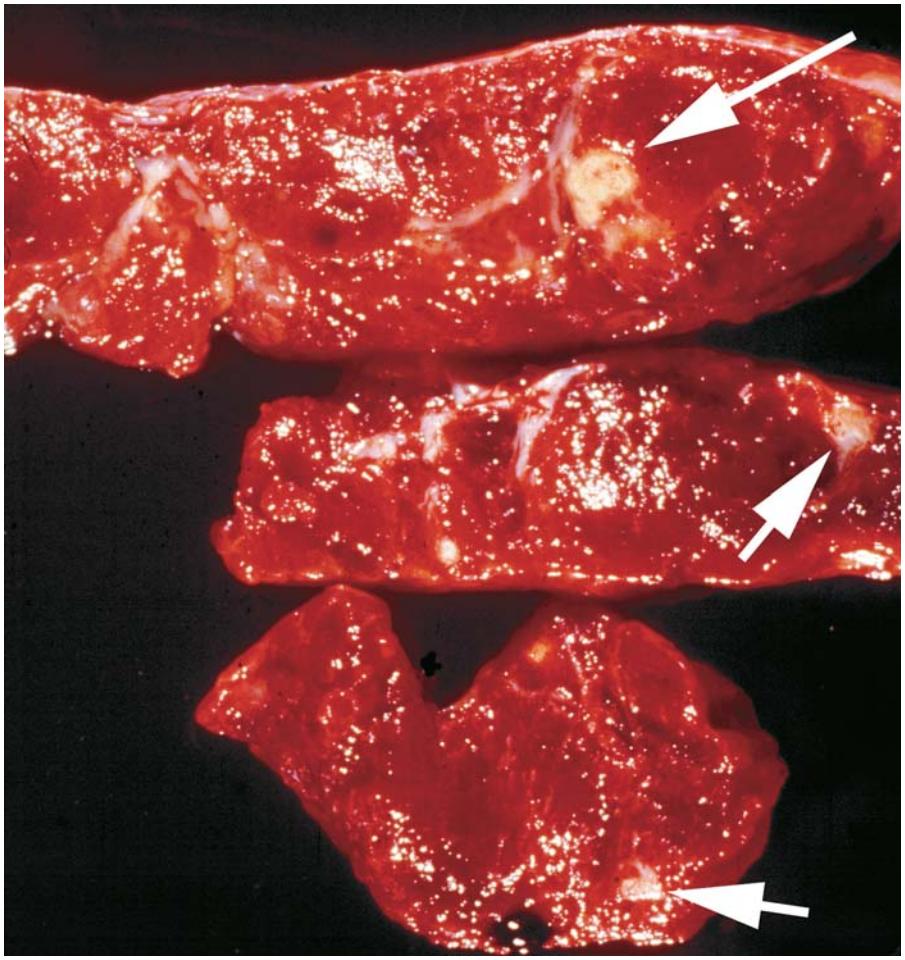

FIGURE 20.28. Numerous placental abscesses (white nodules at arrows) due to *Listeria* infection. Premature infant; immediate therapy with survival.

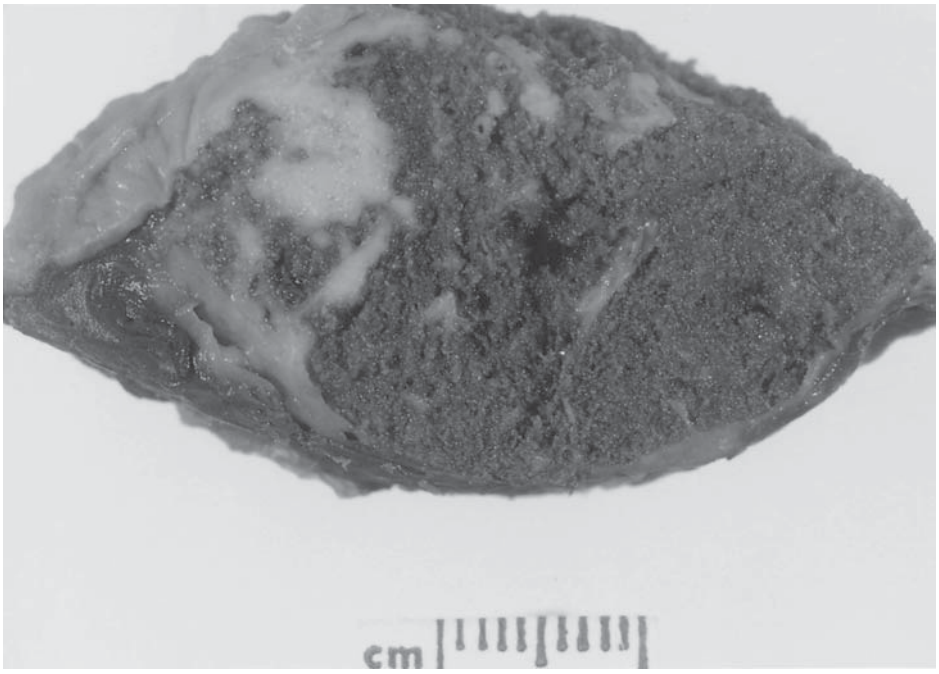

FIGURE 20.29. *Listeria* abscess in the placenta underneath the discolored chorionic plate at 37 weeks' gestation. Maternal fever was immediately diagnosed as due to listeriosis from the smears of the abscess. Ampicillin therapy of the neonate cured the infant who had a diffuse rash at birth.

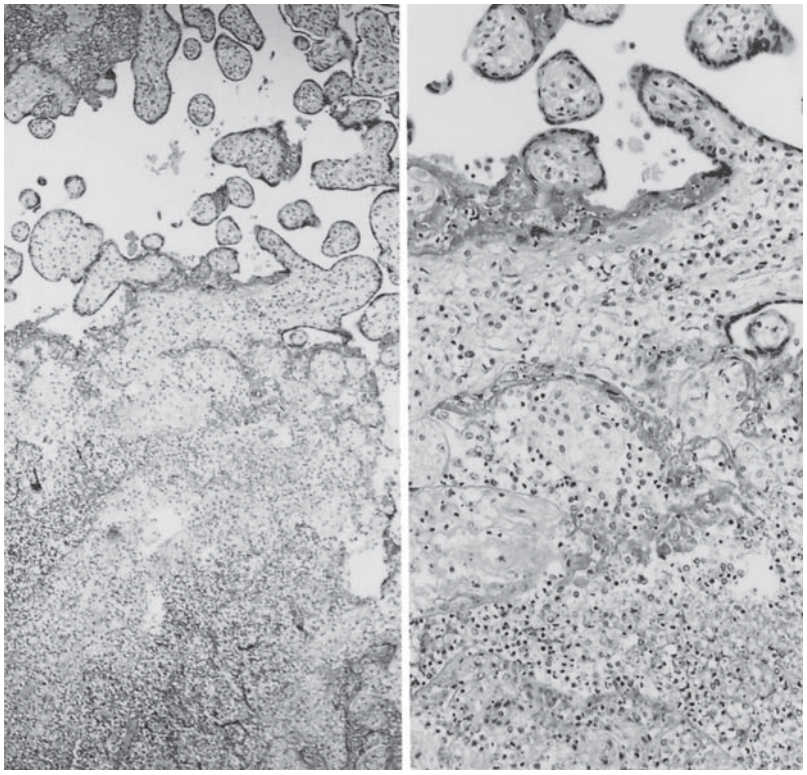

FIGURE 20.30. *Listeria* abscess in an immature placenta of stillborn twins. There is much necrosis of villi, fibrin deposition, and infiltration with PMNLs. Numerous organisms were found on Gram stain. H&E ×60 (left); ×240 (right).

of the placenta prior to examination (Fig. 20.31). The amnionic colonization is so prominent in utero, however, that amniocentesis for the differential diagnosis of febrile patients has been advocated (Petrilli et al., 1980).

When listeriosis is recognized during pregnancy and adequately treated, the placental abscesses undergo scarring. They are then sometimes still recognizable histologically as a former abscess. One must assume that abscesses in the fetus may have a similar fate. Effective therapy during pregnancy has been described by Zervoudakis and Cederqvist (1977) and A.D. Fleming et al. (1985). The latter authors presented another case and described meconium staining and chorioamnionitis. Koh et al. (1980) also saw meconium discharge and found many placental abscesses in a newborn who was severely ill; the infant recovered after ampicillin therapy, which had been commenced prenatally. A similar sporadic occurrence was related by Barresi (1980). The organisms were present in gastric aspirate and on body surfaces. Placental abscesses were present. In another case, treated at 13 weeks' gestation, the placenta and infant were normal when the patient delivered at term (Cruikshank & Warenski, 1989). Identical lesions of placenta and fetus have been described in nonhuman primates (McClure & Strozier, 1975).

Recurrence of listeriosis during subsequent pregnancies has occasionally been described (Rappaport et al., 1960; Dungal, 1961; Ruffolo et al., 1962). Such events and

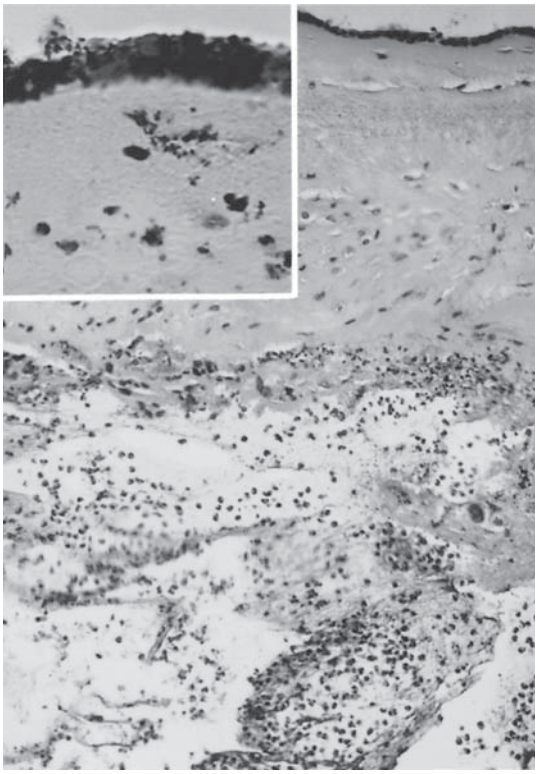

FIGURE 20.31. Listeriosis of the placenta in a stillborn. There is extensive subchorial infiltration with leukocytes, edema of membranes, and massive bacterial growth in amnion. H&E ×160. Inset: Gram stain. ×640.

the unexplained reason for the unusual frequency of severe listeriosis during pregnancy and in newborns have raised questions about the pathogenesis of this disease. Flamm (1959) experimented with rabbits and was of the opinion that septic transplacental infection causes the placental and fetal infection. This opinion is partly supported by the findings of typical abscesses in the placenta and the occasional finding of organisms within intact amnionic sacs. The presence of organisms in the vagina and in stool and the typically severe chorioamnionitis, however, suggest that an ascending mode of infection additionally occurs. Perhaps the placental abscesses form after fetal septicemia has taken place, similar to the abscesses in the fetus. Whether one or both of these modes of infection is the predominant way of fetal infection with listerial organisms is currently not known.

The susceptibility of immunodeficient and pregnant patients may result from their altered T-cell function. Schaffner et al. (1983) addressed this question experimentally by treating mice with cyclosporin A and cortisone, and by infecting nude mice. Their conclusion was that *Listeria* infection is biphasic: "Bacterial multiplication is controlled by nonspecific defense mechanisms in the early phase, and by acquired T-cell–dependent immunity in the second." This question was further explored in the work of Redline and Lu (1987), who found that local, decidual immune response regulated infection of the fetoplacental unit. They suggested an analogy to the nonrejection of the placental graft in regard to this immunologic interaction of *Listeria* and the decidua. In later studies, Redline et al. (1988) found that hormonal induction of deciduomas allows bacterial proliferation in the uterus, but that this endocrine manipulation does not influence the infection of peripheral organs of mice. It was also true when the mice were preimmunized. The investigators then studied the composition of the immune cells in the decidua and found that "increased bacterial titers were correlated with an inability of macrophages and T lymphocytes to reach [the] tissue *Listeria* [organisms] in discrete regions of deciduoma-bearing uteri." They further suggested that an antifetal (placental) immune response of the host was hindered by the same decidual mechanism that allows uncontrolled listerial growth locally (Redline & Lu, 1988). These findings suggested that the lack of recurrent listeriosis transmission by 74 women who had once delivered an infected child (Degen et al., 1970) is not the result of immunization. Bortolussi et al. (1989) found in rat experiments that neonatal interferon deficiency may be responsible for the susceptibility of infants.

Another organism that was reported to have caused the formation of placental abscesses is *Burkholderia pseudomallei*, the gram-negative bacillus causing **melioidosis** (Abbink et al., 2001). The mother had been treated with antibiotics for ulcerative colitis and a placenta previa necessitated cesarean section. The neonate had sepsis and the organism was subsequently cultured from the cervix.

Actinomyces

Only three cases of placental inflammation due to this gram-positive anaerobic organism have been reported (Zakut et al., 1987; Abadi & Abadi, 1996). The infection observed by the latter authors occurred in an afebrile patient at 25 weeks' gestation of a dichorionic twin pregnancy with premature labor. Upon membrane rupture, foul-smelling fluid emerged. Both placentas had marked chorioamnionitis and histologically characteristic organisms. Zakut et al. (1987) had reported two cases with massive invasion by actinomycetes and necrotizing placentitis.

Mycoplasma Hominis *and* Ureaplasma Urealyticum

Mycoplasmas are a well-recognized group of pathogens of many animals. They cause infections of the urogenital tract, are responsible for respiratory and joint diseases, and are a frequent cause of epidemics in laboratory animal colonies (Tully & Whitcomb, 1979). Two organisms, *Mycoplasma hominis* and *Ureaplasma urealyticum* (also known as the "T strain" because the colonies are so tiny) are known urogenital pathogens for humans (Cassel & Cole, 1981); other *Mycoplasma* species affect different organ systems. *M. hominis* is a known cause of PID, febrile conditions during the postpartum period (Naessens et al., 1989), and possibly urinary tract infections. *U. urealyticum* (as well as *Chlamydia trachomatis*) is known to cause nongonococcal urethritis in men (Shepard, 1970; Taylor-Robinson & McCormack, 1980). The organism attaches itself to spermatozoa and may thus more readily penetrate the endocervical mucous barrier (see Fig. 20.24). It is also likely that combined infection with these two organisms is a cause of mucopurulent cervicitis in women (Paavonen et al., 1986). The available evidence suggests that these organisms are sexually transmitted (McCormack et al., 1972). Sterility in women is often secondary to PID, and much direct evidence exists that *U. urealyticum* infection of fallopian tubes is an important cause (e.g., Friberg, 1978). On the other hand, Gump et al. (1984) found that there is no relation between involuntary infertility and *Mycoplasma* infection. Yoon et al. (1998) showed the significant inflammatory reaction that follows infection with ureaplasma.

Kundsin et al. (1967) first suggested that infection with the T strain of *Mycoplasma* may cause chorioamnionitis and repeated abortion. They observed this new strain in cultures from decidua and aborted fetal membranes of a patient who had had four previous unsuccessful pregnan-

cies. The fetal lung contained aspirated pus. Microorganisms were not identified histologically in the inflamed tissues. Additional specimens gave similar results. These observations suggested that this new strain (*U. urealyticum*) may be the cause of repetitive abortions, as well as of sterility. Premature rupture of membranes and premature delivery have recently been associated with both *Mycoplasma* and *U. urealyticum* (Perni et al., 2004). A case similar to that described by these investigators is depicted in Figure 20.32; it is a patient with four previous abortions. Severe chorioamnionitis in this abortus is evident from the opacity of the fetal surface. Subsequent treatment with antibiotics of this patient and her husband resulted in a healthy term pregnancy (Quinn et al., 1983).

Since the initial description of placental infection with *Mycoplasma*, there have been numerous clinical and pathologic studies that aimed to define the roles of these pathogens in reproductive failure of women, specifically attempting to relate them to PROM and chorioamnionitis. Some conflicting results have been obtained. The studies are hampered by the facts that these organisms have specific culture requirements and cannot be identified by routine microscopic examination of tissues. Prenatal infection of fetal tissues has been demonstrated microbiologically in many studies, but positive antepartum cultures do not predict outcome effectively (Carey et al., 1991). Furthermore, erythromycin treatment of infected women does not apparently prevent premature delivery (Eschenbach et al., 1991). Both organisms are a cause of neonatal meningitis (Waites et al., 1988); *M. hominis* has been the cause of neonatal lung abscess (Sacker et al., 1970), and *U. urealyticum* infection has been associated with chronic neonatal lung disease (Cassell et al., 1988; Sanchez & Regan, 1988; Wang et al., 1988).

Madan et al. (1988, 1989) made detailed microbiologic studies of autopsy and placental material; they found that "genital *Mycoplasma* were isolated from 36 cases (8.3%), and acute chorioamnionitis and funisitis were present significantly more often in cases with genital mycoplasmas." In their detailed study of perinatal deaths, including isolation of various pathogens from placenta and neonatal lung, they came to similar conclusions. One of their stillborns had myocardial calcifications, and some not only had aspirated pus in the lung but also an interstitial chronic inflammatory response, suggesting prolonged exposure to this mycoplasmal antigen. In this decisive pathologic study of perinatal infection with this organism, the authors were much impressed with the attending villous edema in the placenta.

The disease caused by these organisms is similar to that of other acute infections, except for the absence of demonstrable bacteria. The chorioamnionitis is similar as well. There have been some other suggestions that mycoplasmal infection causes villous alterations. Kundsin et al. (1967) found "unusual sclerosis of villi"; and Romano et al. (1971), who described aspiration bronchopneumonia in an aborted 19-week fetus with isolation of T-strain organisms, described degenerative changes of villous vessels, thrombosis, and villous edema. The illustration accompanying their article, however, depicted normal architecture. This study, as many others, was hampered by our current inability to demonstrate the organism microscopically in tissue sections. In the future it will require special techniques, such as study with immunofluorescence.

The relation of *Mycoplasma* to PROM, premature labor, and chorioamnionitis is still debated; Romero et al. (1989c,d; Romero, 1989) have critically reviewed 12 published studies to assess this relation. They criticized several of them as being indecisive and poorly designed. Their

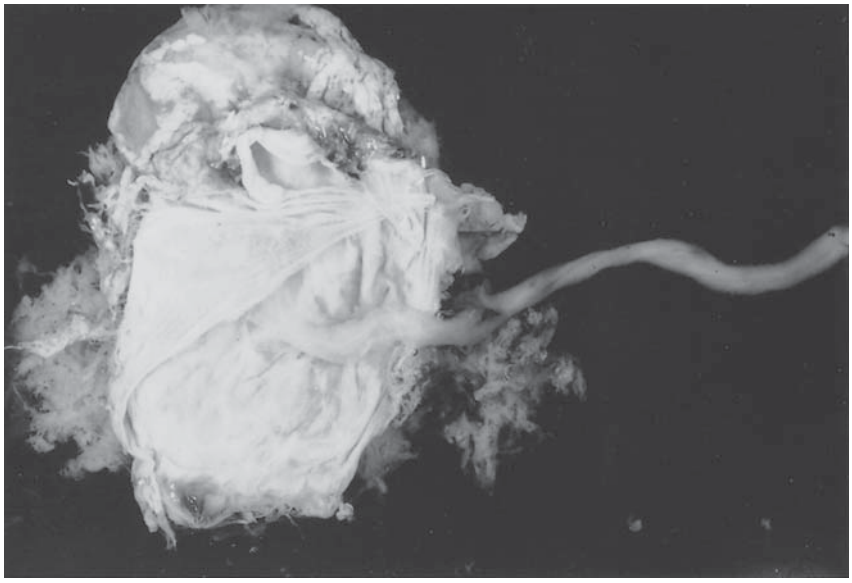

FIGURE 20.32. Placenta of spontaneous abortion due to *Ureaplasma urealyticum* infection. The patient had had four previous abortions with similar morphology. Note the creamy pus underneath amnionic surface, and fresh marginal hemorrhage.

opinions are that the association of cultured organisms and PROM "does not prove a cause-and-effect relationship," and when all studies were analyzed in detail, "it seems unlikely that genital colonization with *Mycoplasma* species without a failure of the host defense (fetal and/or maternal) leads to preterm delivery." This report was criticized by Kundsin and Horne (1989), and the reply must be read to appreciate the controversies, especially with respect to effective therapy.

In a prospective cohort study of 6500 women, no association of *U. urealyticum* infection with premature labor was found by Nugent et al. (1988). Pathologic and microbiologic studies on neonates from patients with and without chorioamnionitis by Quinn et al. (1987) established a strong correlation between *U. urealyticum* colonization and chorioamnionitis. Kundsin et al. (1996) found that prenatal infection with this organism increases significantly the longer the membranes have ruptured. They emphasized that eradication of the infection in a gravida should be attempted. Gauthier et al. (1994) felt that isolation of the organism would not lead automatically lead to delivery, and they treated women successfully with erythromycin. When maternal antibody response was taken into consideration, Gibbs et al. (1986) found a strong correlation of a pathogenic role of *M. hominis* infection. Considering the frequently mixed nature of infection, the high prevalence of some of these organisms, and the differences in the composition of the populations studied, it is presently impossible to come to a clear-cut decision. Our impression is that the genital mycoplasmas are pathogenic genital organisms, and that they are a frequent cause of chorioamnionitis and premature birth. In fact, several studies have shown that they are the principal organisms isolated from the placental surface and amnionic fluid of patients with PROM.

Chlamydia Trachomatis *and* C. Psittaci

The genus *Chlamydia* has several species (Peeling & Brunham, 1996). Of these, *Chlamydia psittaci* causes parrot fever (psittacosis), and *Chlamydia trachomatis* is responsible for the most common sexually transmitted disease in the United States (see also Gaydos et al., 1998; Peipert, 2003). It also causes trachoma, lymphogranuloma venereum, nongonococcal urethritis in men, and the diseases in women that will next be discussed. *Chlamydia pneumoniae* and *C. pecora* are now considered to be subdivisions of *C. psittaci* and have not yet been assigned as being gestational pathogens. It is estimated that between 10% and 20% of sexually active men and women are infected with one of these organisms (Saxer, 1989; Caul et al., 1997; Miller, 2005). Ryan et al. (1990) surveyed a large population of women by cervical culture and found that 21.08% were positive. They recommended routine culture for *Chlamydia*. Approximately half the infants born to infected mothers develop ophthalmia neonatorum ("inclusion body blenorrhoea"). Others develop pneumonitis. It is estimated that 3% to 4% of neonates have ophthalmia, and 1% to 2% have pneumonitis from infection with this organism (Harrison et al., 1978; Harrison, 1985).

The bacterium-like intracellular microbe can be visualized in the cytoplasm of infected cells by direct immunofluorescence study. *Chlamydia* has also been isolated from neonates, even from the pneumonia of stillborns infected through intact membranes (Thorp et al., 1989). Other than by culture, the infection can be diagnosed in infected tissues and amnionic fluid with the immunoperoxidase technique, as employed by Shurbaji et al. (1988), and by DNA sequences following polymerase chain reaction (PCR) amplification (Pao et al., 1991). The direct immunofluorescence technique has a sensitivity of approximately 89% (Binns et al., 1988), and fine-tuning allows some additional improvement (Pastorek et al., 1988). Livengood et al. (1988) investigated various staining methods and emphasized the diagnostic importance of having experience when reading the slides. An enzyme immunoassay was advocated by Binns et al. (1988) as being highly sensitive and therefore a good diagnostic test. Reports on the prevalence of the disease must be interpreted with these limitations in mind. But new, simple, and effective methods for detection (e.g., polymerase and ligase chain reactions) have been added to the armamentarium of epidemiologists (Pasternack et al., 1996; Andrews et al., 1997; Locksmith, 1997) that should much improve diagnosis and results from surveys. Thus, PCR from self-obtained samples of the introitus yielded excellent results (Wiesenfeld et al., 1996).

Chlamydia trachomatis infection of the cervix, where it causes mucopurulent cervicitis (Brunham et al., 1984, illustrated in color by Peipert, 2003), is also relatively easily demonstrated by the use of the direct fluorescence method (Graber et al., 1985). Brunham et al. (1984) provided impressive color photographs of the stained organisms. *C. trachomatis* is responsible for a significant number of cases of acute salpingitis (Magnusson et al., 1986), and it also causes chronic salpingitis and sterility (Guderian & Trobough, 1986; Moss et al., 1986). The effect of a *C. trachomatis* infection on pregnancy is still controversial. Sweet et al. (1987) reported that PROM was more likely to occur when infection had caused a maternal antibody response, but statistical significance was not reached. Alger et al. (1988) found that the organism was isolated from 44% of patients with PROM but only in 16% of controls. There are suggestions that PROM and perhaps chorioamnionitis are linked to this infection, but much more direct evidence needs to be marshaled before such a conclusion can be affirmed. The organism has not been isolated from the placenta, but has been demonstrated in amnionic fluid, and in the eye and nasopharynx of neonates (Thomas et al., 1990). It has also not yet been demonstrated conclusively to be a direct cause of

chorioamnionitis, except in rat models (Rettig & Altshuler, 1981). Ryan and his colleagues (1990), however, accumulated data on the infection in pregnancy that suggested premature rupture of membranes to be much more likely when the infection was not treated. Other investigators support the notion that chlamydial infection in pregnancy should be treated with antibiotics (Forster et al., 1991; Crombleholme et al., 1990).

Chlamydia psittaci infection is rarely recognized as a cause of human abortion, although this infection commonly causes abortions in sheep and other domestic species. Initial infection is sheep is followed by a 30% abortion rate that later declines to 5% when the flock is thoroughly infected (Gunson, et al., 1983). Reports by Johnson et al. (1985) and Wong et al. (1985) indicated that sheep farmers and their wives have a high exposure to this pathogen. A pregnant wife of a farmer became infected and aborted at 28 weeks' gestation. Acute intervillositis was found in the grossly normal-appearing placenta. Syncytiotrophoblastic inclusions were present that showed numerous organisms by ultrastructural study and positive immunofluorescence. The fetus was also infected with organisms recovered from various organs. We have summarized the experience with such an infection (Hyde & Benirschke, 1997; Jorgensen, 1997). This abortion occurred following a febrile episode in a woman who had assisted with lambing. The sheep were later found to be chronically infected with this organism. Characteristically, the patient's DIC ceased after abortion of the infected placenta. In one instance, at least, the pregnant patient succumbed from the disease. The placenta had massive intervillous leukocyte accumulations, villous necroses, and the typical presence of masses of chlamydial organisms that appear to preferentially proliferate in the cytoplasm of the syncytiotrophoblast (Fig. 20.33A–D). Since that report another experience with abortion in pigs due to this agent has been published (Thoma et al., 1997).

Bacterial Vaginosis

Bacterial vaginosis has been defined by Westrom et al. (1985) as the "replacement of the lactobacilli of the vagina by characteristic groups of bacteria accompanied by changed properties of the vaginal fluid." The other bacterial species include *Bacteroides, Gardnerella vaginalis, Mycoplasma hominis, U. urealyticum,* and perhaps others. A relation to PROM and amnionic sac infection has been reported to exist (Gravett et al., 1986). Many authors since have suggested that bacterial vaginosis is a common cause of intraamnionic infection and premature birth (Silver et al., 1989; Hillier et al., 1995; Newton et al., 1997). Consideration of this entity, however, is beyond the scope of this chapter; suffice it to say that current opinion is that systemic antibiotic therapy is required and effective (Hauth et al., 1995; Joesoef et al., 1995; McGregor & French, 1996). An extensive review has been provided by Martius and Eschenbach (1990) that considered the relation of vaginosis to chorioamnionitis, and numerous clinical publications have also considered this topic. A relation to preterm labor was shown by Subtil et al. (2002) and a meta-analysis by Leitich et al. (2003) showed it to be "a strong risk factor for preterm delivery and spontaneous abortion." Therapeutic trials of antibacterial treatment have been effective in reducing preterm births (Ugwumadu et al., 2003).

Syphilis

Infection with *Treponema pallidum* may occur at any time during pregnancy. The organism may pass to the fetus through the placenta during all stages of maternal syphilis infection. The responsible organism is a 4 to 10 μm long, 0.5 μm wide spirochete. According to Grossman (1977), "Most frequently, dissemination is associated with a placentitis arising from hematogenous spread of the spirochetes between the first and second stages of infection of the mother." The commonly held notion that the placenta is impermeable to spirochetes before the 20th week of pregnancy, because of the thickness of Langhans' cytotrophoblast layer (Fiumara, 1975), can no longer be accepted. Braunstein (1978) described a spontaneous abortus (12.8-cm CR length, approximately 4.5 months' gestation) with an abundance of spirochetes in the liver and other organs and marked placental changes. We had shown, by immunofluorescence and electron microscopic studies, that spirochetes can be demonstrated in fetuses as early as at 9 to 10 weeks' gestation (Harter & Benirschke, 1976). One reason why prior studies had failed to identify fetal syphilis is because the expression of the disease's features depends on the fetus's ability to react with antibody production to the spirochetal antigen. Histopathologic changes cannot be seen before that developmental time, and the disease is thus not diagnosed. Ohyama et al. (1990) have since demonstrated spirochetes in syphilitic placentas by the immunoperoxidase technique, and Nathan et al. (1997) also isolated spirochetes from early gestations and subsequently successfully treated the fetuses. Although spirochetes may be difficult to identify, a variety of new techniques are now available. The study of congenital syphilis by Guarner et al. (1999) describes histochemical means by which to demonstrate an abundance of spirochetal remnants in this disease, aside from complete spirochetes, thus making diagnosis considerably easier.

The relation of infection to disease was first clearly elucidated by Silverstein (1962) and Silverstein and Lukes (1962). They found congenital syphilis with attendant fetal plasma cell infiltration and reasoned that the inflammatory response was the cause of illness. Another reason for lack of recognition of early fetal infections is that it is

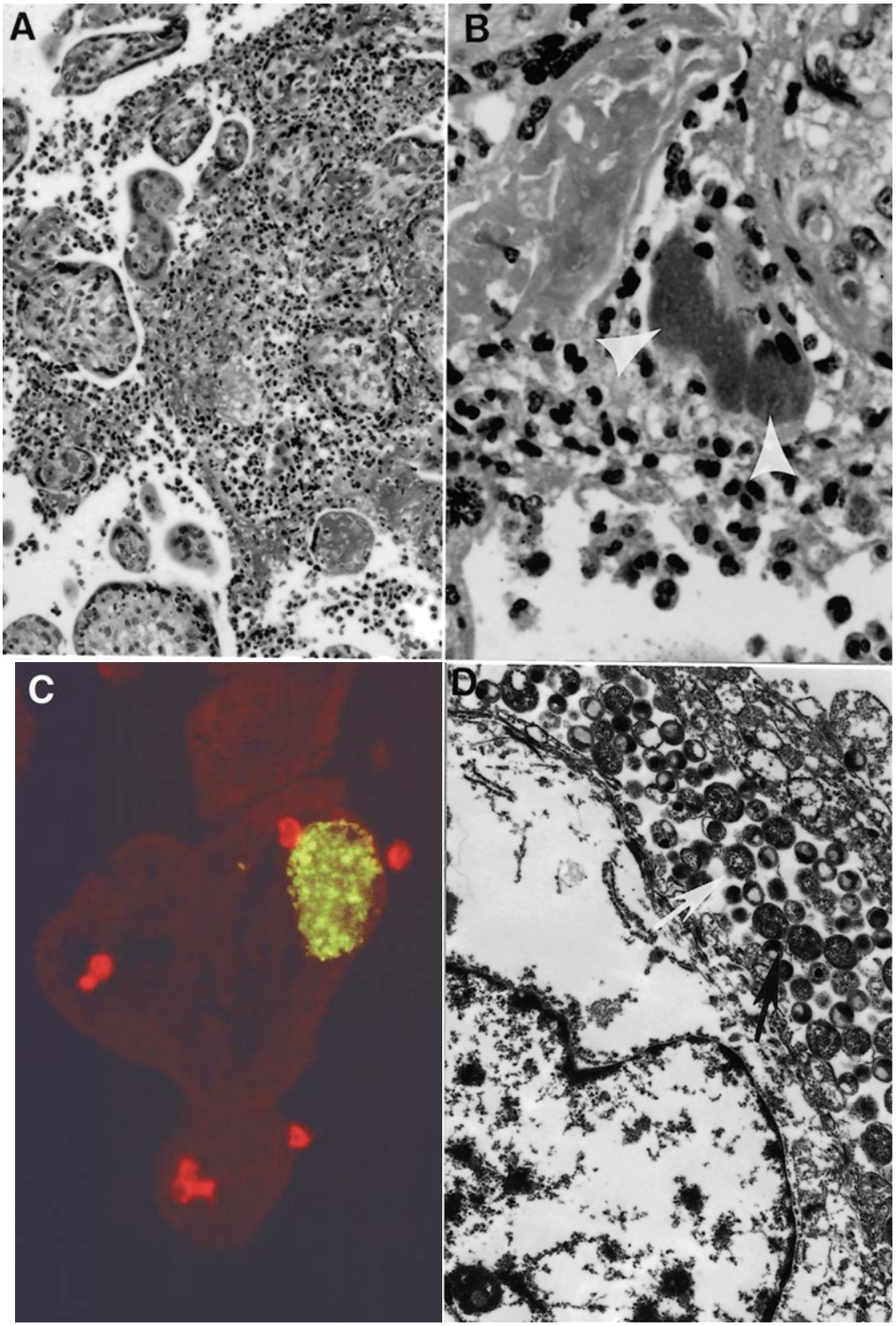

FIGURE 20.33. A: Acute intervillositis (abscess) with villous destruction in *Chlamydia psittaci* infection. B: Cluster of organisms in syncytial cytoplasm at arrowheads. C: Immunofluorescent localization of antigen. D: Electron microscopic (EM) demonstration of syncytial organisms. (A,B: H&E ×100, ×400; C: immunofluorescence ×400; D: EM ×1500) arrow at organism. (*Source:* Modified from Hyde & Benirschke, 1997.)

often difficult to demonstrate spirochetes histologically. Fetuses from such infections are often macerated, and radiographic study of long bones, often diagnostic of the infection, is frequently neglected. The disease may also appear as hydrops fetalis (Barton et al., 1992). The treponemes in macerated fetuses are most abundant in the liver; they are rare in the placenta and umbilical cord. Wendel et al. (1989, 1991) have shown that in gestations with fetal death from syphilis, darkfield examination of amnionic fluid always readily allows demonstration of treponemes. In addition to the conventional silver stains, it has been demonstrated that spirochetes may be stained with immunofluorescence in formalin-fixed tissue (Hunter et al., 1984). Thus Epstein and King (1985) demonstrated spirochetes in macerated liver tissue by immunofluorescence. Nevertheless, improved Warthin-Starry silver stains are probably the best means of identifying spirochetes in tissues (Kerr, 1938). It has now been established also that the organism can be identified in macerated fetuses with the Warthin-Starry stain (Young & Crocker, 1994).

A classic paper of the neonatal pathology in congenital syphilis was written by Oppenheimer and Hardy (1971). They confined their report to 16 neonatal deaths and did not consider the 31 macerated fetuses they saw during the same time. Hepatosplenomegaly was found in all, but after penicillin therapy spirochetes were not demonstrable with the Levaditi stain. The report does not include a consideration of placental lesions. Judge (1988) also provided an excellent review of congenital syphilis, with emphasis on the stage of pregnancy when the disease was acquired.

Many morphologic changes are found in the placenta and umbilical cord with congenital syphilis (Russell & Altshuler, 1974; Horn et al., 1992). By and large, the more severely the fetus is affected, the greater are the pathologic changes in the placenta. A macerated fetus with congenital syphilis may have a massively enlarged placenta with numerous pathologic features; a general increase in placental weight has been demonstrated by Malan et al. (1990). Most authors who have studied the placenta of congenital syphilis have concluded that there are no absolutely characteristic pathologic findings, but bulky villi and some other changes to be discussed should raise the suspicion. When suspicion of fetal syphilis exists, silver preparations for spirochetes are indicated. They may ultimately prove that lesions are due to syphilis when other means such as serology and radiographs of the fetus are not available. It must be cautioned, however, that the stains are not always easy to execute and that incomplete treatment with antibiotics may prevent identification of spirochetes. Fojaco et al. (1989) have claimed that necrotizing funisitis is a specific lesion of congenital syphilis and Knowles and Frost (1989) have expressed a similar view. Discussion of this fallacy is included in the next section of this chapter. Because much of the informative literature on placental syphilis comes from an era when the other causes of banal types of chorioamnionitis and funisitis were not recognized, the early literature must be interpreted with caution.

When congenital syphilis was suspected in the past, physicians made scrapings of the umbilical venous intima for darkfield examination; and in the discussion of congenital syphilis by Ricci et al. (1989), beautiful silver preparations of this type were illustrated. They also showed the plasma cell villitis in such a case. Hörmann (1954) has reviewed this and other aspects of syphilis in great detail. Baniecki (1928) is one of many authors who sought treponemes in umbilical cords. He found inflammation in five of 14 living infants with syphilis; 12 of 17 stillborns had such inflammation, and five of 40 nonluetic infants had umbilical phlebitis. During the same year, Kaufmann (1928) found no placental lesions in two thirds of children with positive spirochetal infection. Beckmann and Zimmer (1931) made another detailed study of umbilical cords in syphilis. They had 420 cases, of which 392 were at term gestation, including nine stillborns; 28 were premature, including five stillborns. They found inflammation in 18.3% (77 cases; 25 only mild). Of these cases, only three infants had congenital syphilis. Conversely, 13 infants with congenital syphilis had no inflammation. They concluded that funisitis was not characteristic of syphilis but rather was a nonspecific inflammation that was perhaps caused "mechanically." Organisms are also readily identified in amnionic fluid (Wendel et al., 1989, 1991). In some cases of funisitis due to spirochetal infection we found the organisms only peripheral to the exudate and the necrosis, employing the Warthin-Starry stain.

The villous tissue has somewhat more characteristic changes with congenital syphilis. In Braunstein's (1978) 4 months' gestation fetus, the placenta had enlarged villi with endothelial and fibroblastic proliferation. Few mononuclear cells were present. The cellularity of the villi demonstrated in his photomicrographs, however, is impressive and is similar to that shown in Figure 20.34. McCord (1934) had described these features of villous "crowding" and enlargement of the placenta. Russell and Altshuler (1974) were also impressed with the placental enlargement, a feature already commented on by Hörmann (1954), who had referred to a case with a placental weight of 2500 g accompanied by a fetus weighing 2600 g. Russell and Altshuler's diagnostic features included relative villous immaturity, decidual plasma cell infiltration, perivascular fibrous tissue proliferation, and alterations of capillary endothelium. They also found plasma cell infiltrations in the enlarged villi of syphilitic placentas, a finding made repeatedly by us. These changes are all nonspecific. The nature of the infiltrating inflammatory cells within villi has been controversial. Most recently, they

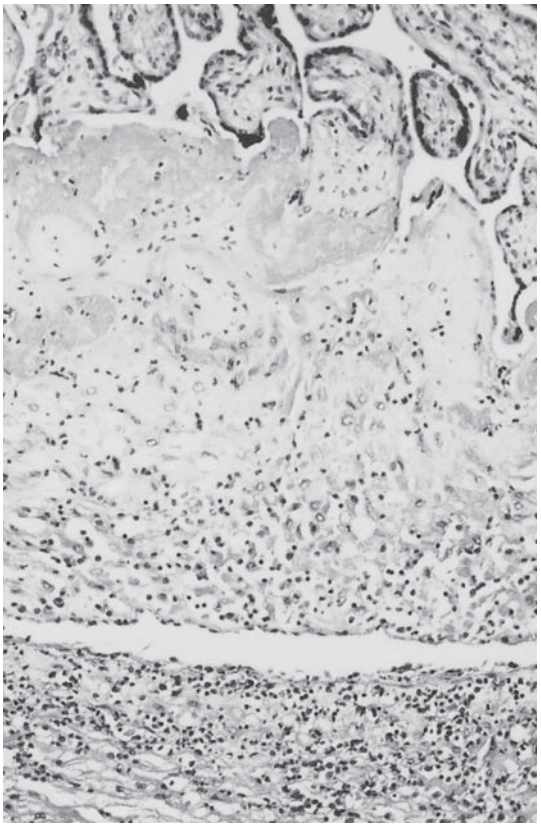

FIGURE 20.34. Plasma cell infiltration of decidua basalis in a placenta of 28 weeks' gestation and an infant afflicted with typical congenital syphilis. The placenta was large 580 gm. H&E ×160.

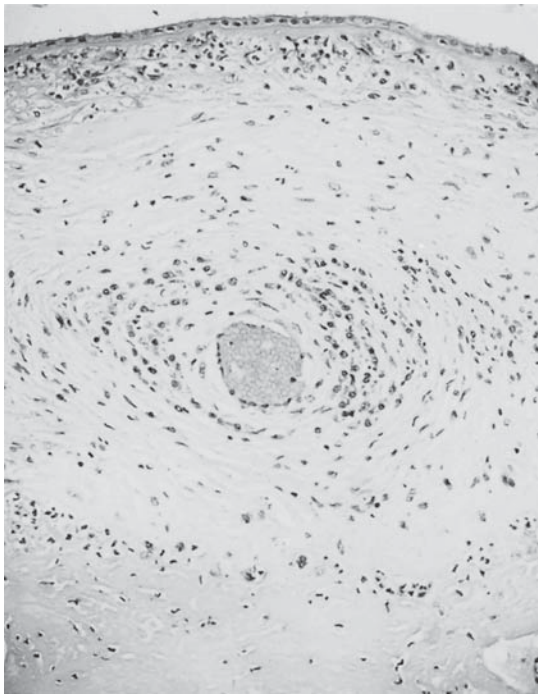

FIGURE 20.36. Perivascular plasma cell infiltration of chorion in congenital syphilis at 30 weeks' gestation. Mild chorioamnionitis is also present. H&E ×160.

were characterized by Kapur et al. (2004) and found to be largely (or exclusively?) of maternal origin. CD3 lymphocytes predominated in that study. Gummas or granulomas have never been reported in the placenta, but Hörmann depicted villous abscesses that had also been seen in earlier studies. In our experience, the villous enlargement is often striking and there are frequent decidual infiltrations with plasma cells; foci of decidual necrosis are common (Fig. 20.35). Abscesses or villous necrosis is frequent in severe infections and chorioamnionitis may be present, but it is also often absent. When it is found, it may include plasma cells, which is an otherwise unusual finding in banal chorioamnionitis (Fig. 20.36). Spirochetes can be found, but often it requires a

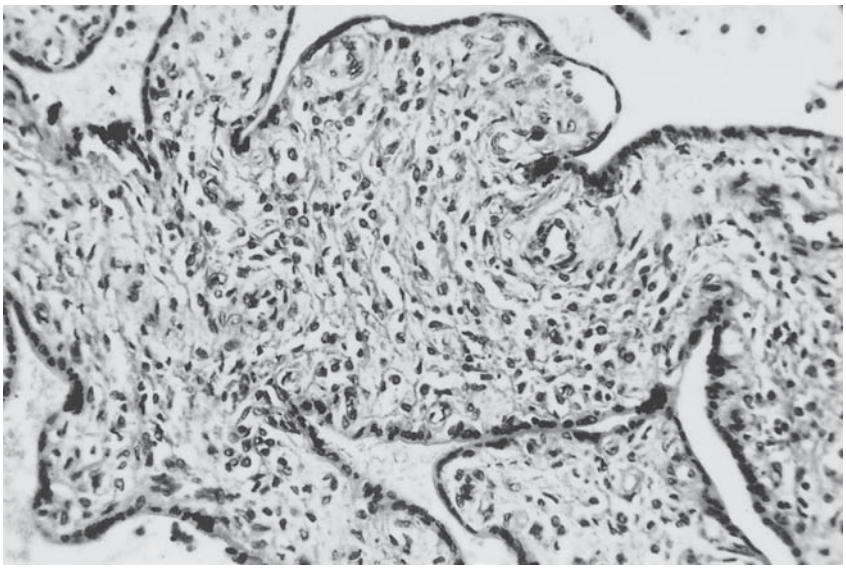

FIGURE 20.35. Villi of placenta in congenital syphilis (same case as in Figure 20.38). Villi are hypercellular, infiltrated with mononuclear cells. Note the focal necrosis and vascular obliteration. H&E ×240.

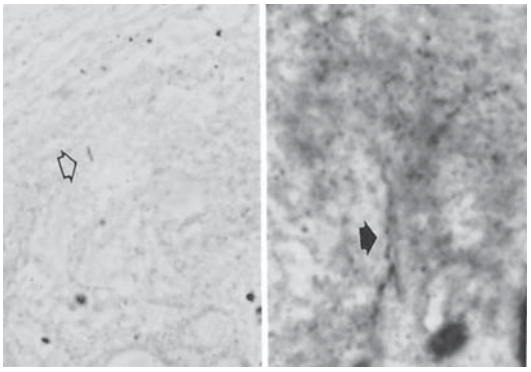

FIGURE 20.37. Spirochete (arrows) in the placenta of stillborn infant with congenital syphilis. Levaditi stain. ×1600.

prolonged search (Fig. 20.37). Moreover, and regrettably, the art of staining spirochetes in tissues is gradually being forgotten by histologists. There is a reported decrease of estriol production by the placenta in syphilis (Parker & Wendel, 1988), perhaps due to a possible decrease in fetal adrenal androgen precursors, rather than to a placental inability to aromatize androgens.

Necrotizing Funisitis

The term **subacute necrotizing funisitis** was introduced by Navarro and Blanc (1974) in a report of 16 cases. In the earlier literature this condition had been referred to as "phlegmonous funisitis" (see Hörmann, 1954). It is an infrequent and unusual type of a more chronic inflammation of the umbilical cord in which even calcification of the old exudate may occur. Calcifications of the umbilical cord had only rarely been reported before the descriptions by Navarro and Blanc. Eight of their cases were stillborn infants. With the exception of two isolations of *Candida* species, no pathogen was identified. Syphilis and other specific agents were carefully excluded by serology in that study. The umbilical cords of these infants had severe inflammation deposited in "successive waves." It was present in a ring-like fashion around the umbilical cord vessels. The exudate was often degenerated and had become calcific. Mural thrombosis was present in several vessels. Two infants had an uncommon presence of plasma cells in their umbilical cord. The nature of the exudate indicated that it is a chronic infection, as did similar inflammatory changes in the lungs of several stillborns. Other signs of chronic infection were found in the stillbirths, and they occurred during the neonatal life of survivors. Chorioamnionitis with frequent surface necrosis was invariably additionally present. In the opinion of Navarro and Blanc, the funisitis differed in severity and chronicity from the usual type of funisitis found in the amnionic sac infection syndrome. Miyano et al. (1998) suggested that it represents the end of the infectious process, where only immune perturbations still exist.

Perrin and Bel (1965) had previously described three cases of cord calcification, one of which, however, may have originated in a hematoma. In one of these cases, there was difficulty in clamping the cord at delivery. An interesting aspect of this inflammation was the "neovascularization" of the exudate, with the origin of these capillaries being unknown. Schiff et al. (1976) described calcification of all three vessels in the cord and had even visualized it sonographically before birth. As in other cases, the calcifications followed the cord vessels, but they stopped before entering the abdomen of the infant. This observation is important, as it further clarifies the pathogenesis of chorioamnionitis and funisitis. It indicates the presence of antigen within the amnionic sac and negates the opinion that the umbilical vasculitis results from a systemic infection. No inflammation was described in their case, but the fetal growth restriction was thought to be secondary to the restriction of blood flow. Gille (1977) described a similar case and drew attention to the fact that granulation tissue was present in the vessels. The patient was a premature infant who did well. The exudate accompanied the vessels for the length of the cord, and a fresh thrombus was present within the vein. The accompanying photographs showed an impressive and uncommon amount of inflammation and "organization," which is otherwise rare in the placental vasculature. Knowles and Frost (1989) have added a case report of necrotizing funisitis in congenital syphilis with organisms plentiful in this lesion but sparse elsewhere.

Numerous cases of chronic, necrotizing funisitis have been seen by us. Some had calcifications, but others did not. In our view, they represent different stages in the evolution of funisitis. Figure 20.38 shows a cross section of umbilical cord in an immature placenta with necrotizing funisitis. Figure 20.39 shows the concentric rings of white exudate in a growth-retarded infant at 31 weeks; in contrast to the previous case, here the inflammatory reaction totally surrounds the vessels. In Figure 20.40, a radiograph shows the peripheral calcification that has formed in the old exudate. Numerous plasma cells were found in the inflammatory debris, but electron microscopic search for organisms was unrewarding. The mother had had a febrile illness during the first trimester, but otherwise mother and infant were entirely normal. In other cases, herpes virus II antigen could be localized to such cords with specific antibodies (Robb et al., 1986b).

Craver and Baldwin (1992) reviewed 60 cases of this necrotizing funisitis, 45 of which had clinical information. This is clearly the largest case collection of this lesion. It occurred in 0.1% of deliveries more than 20 weeks' gestation. Growth restriction (28%), stillbirths (18%), and necrotizing enterocolitis (22%) were prominently associated problems. These investigators did not find any single agent

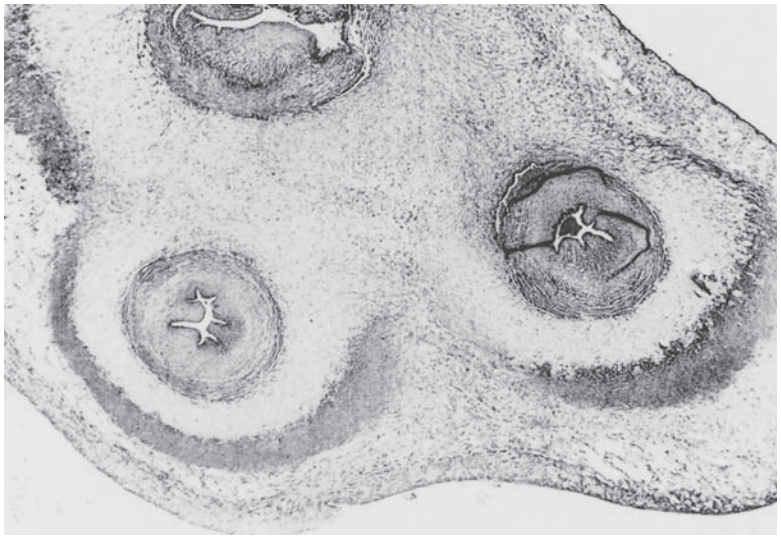

FIGURE 20.38. Umbilical cord at 31 weeks' gestation with chronic inflammatory exudate (necrotizing funisitis). The exudate is concentrically deposited around the vessels; much old exudate is necrotic and beginning to calcify. A partially organized mural thrombus is present in the umbilical vein. The patient had rupture of the membranes for more than 12 hours, a circumvallate placenta, and massive chorioamnionitis. von Gieson. ×12.

or maternal condition that caused chronic funisitis. Calcification was present in 47% of their cases and chorioamnionitis in 98%. The investigators suggested that a diffusible toxin in the amnionic cavity might cause this lesion because of its similarity to an Ouchterlony immunodiffusion plate. As stated earlier, Fojaco et al. (1989) suggested that necrotizing funisitis "permits a presumptive diagnosis of congenital syphilis at birth." They referred to the gross appearance as a "barber-pole cord" and found 16 cases of this association with congenital syphilis. All their cases of necrotizing funisitis were in luetic pregnancies, and spirochetes were found in four of 10 patients. Fojaco and her colleagues stated that information in the early literature suggests that necrotizing funisitis is diagnostic of syphilis. In fact, however, Hörmann (1954) had extensively studied syphilis and funisitis, and he did not find an absolute relation between these conditions. It is true that funisitis often occurs in syphilis, but not so regularly as suggested. Hörmann and other authors have also often found necrotizing funisitis in nonsyphilitic pregnancies. This point was well made by Craver and Baldwin (1992), with whom we agree. In some umbilical cords with necrotizing funisitis, we have identified herpes antigen, to be discussed below. Thus, necrotizing funisitis is a chronic, severe inflammation of the cord, frequently associated with calcification, and caused by immune reaction to presumably several different antigens. Likewise, Jacques and Qureshi (1992) found this not to be a strong association, when they studied 45 cases. Like other investigators, they found *Candida*, *Streptococci*, and other bacteria to be responsible. The necrotizing funisitis is merely the manner by which the umbilical cord can express its chronic inflammatory damage, not being able to remove the debris efficiently that accumulates with chronic exudation. The connective tissue cells of the umbilical cord often degenerate completely with this reaction.

Other Spirochetal Diseases

Leptospirosis, an infection due to one of several species of *Leptospira*, has rarely been reported in pregnancy. Coghlan and Bain (1969) have gathered the few reports of abortion that were presumed to result from this infec-

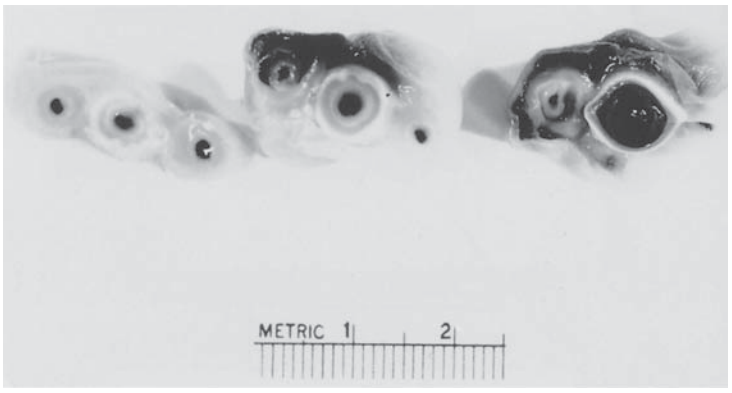

FIGURE 20.39. Concentric rings of perivascular exudate in necrotizing funisitis. There was marked chorioamnionitis in this 31-week pregnancy.

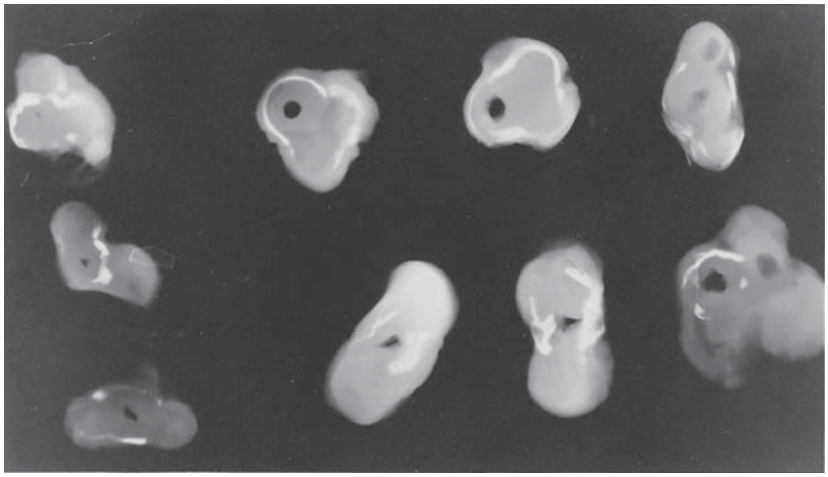

FIGURE 20.40. Radiographic appearance of calcific rings in a cord with necrotizing funisitis. A term, normal infant was delivered. There was no history of maternal problems except a febrile illness during the first trimester. (Courtesy of Dr. R.R. Oldham, Nashville, Tennessee.)

tion; they described the pregnancy of a patient who was infected with *L. canicola*, acquired from a pig. The mother delivered a macerated fetus. Organisms were not recovered from the fetus or from the placenta. Moreover, there were no histopathologic lesions. Abortion due to leptospirosis is said to be a common disease in China, with organisms having been recovered from the affected fetuses.

Borrelia, the spirochetal organism that causes relapsing fever, has been isolated from the blood of a febrile mother and her newborn infant who died shortly after birth (Fuchs & Oyama, 1969). The placenta was not described. The infection follows the bite of an infected tick and the disease is geographically widespread (e.g., Oregon: case just cited; Israel: Yagupsky & Moses, 1985). Shirts et al. (1983) reported a nonfatal case of congenital borreliosis in a febrile patient from Colorado. The spirochetes were depicted in the neonate's blood smear, placental villous capillaries, and umbilical artery. Placental lesions were not described.

Lyme disease (erythema migrans) is an emerging borreliosis of epidemic proportion in the northeastern United States (Athreya, 1989; Eichenfield, 1989; Lastavica et al., 1989; Steere, 1989). This infection, caused by *Borrelia burgdorferi*, has been encountered in other parts of the United States and Europe as well. Transplacental infection was reported in Wisconsin by Schlesinger et al. (1985) and in Utah by MacDonald et al. (1987). In the macerated stillborn of the latter case, the placenta was not enlarged and had "rare plasma cells in isolated villi." The specimen was grossly unremarkable. Spirochetes were identified in the fetus and placenta by special stains. The placental histology showed such excess of erythrocyte precursors (in the fetal circulation) that it could easily have been mistaken for erythroblastosis fetalis. In these two cases, the fetuses had congenital anomalies. Hemminki and Kyyrönen (1989) found an overrepresentation of gastrointestinal atresias in offspring from animal caretakers and forestry and agricultural workers. They suggested that infection with *B. burgdorferi* may be an etiologic factor. The review of Steere (1989), however, suggested that there is no causal relation between this infection and anomalies. The same assertion was made by Strobino et al. (1993), who undertook a prospective study and found neither a definite increase of fetal anomalies nor adverse pregnancy outcomes.

Abramowsky et al. (1991) found nontreponemal spirochetes primarily in the intestines of four spontaneously aborted fetuses with chorioamnionitis, severe chronic villitis, and villous vasculitis in some. It was possible to rule out *Treponema*, *Borrelia*, *Leptospira*, and *Campylobacter*, and the precise nature of this organism remains to be determined. Infections with *Ehrlichia* have also been delineated, and are discussed below.

Fungus Infections

Candida albicans infection of the vagina is common during pregnancy. Oriel and colleagues (1972) estimated that 26% of women harbored yeast: *C. albicans* in 81%; *Torulopsis* (*Candida*) *glabrata* in 16%. The use of oral contraceptives increased the frequency. Peeters et al. (1972) reported similar results. They opined that an increased use of antibiotics, contraceptives, and trichomonacides may be responsible for this frequency. Bret and Coupe (1958) demonstrated that neonatal fungal infection (mostly candidiasis) can be traced to maternal vaginal infection in most cases. The organisms usually then disappear spontaneously for unknown reasons.

Prenatal infection of placenta, cord, and fetus has been reported in hundreds of cases since its first description (Benirschke & Raphael, 1958; Whyte et al., 1982; Qureshi et al., 1998). Figure 20.41 illustrates a classical case. The patient was a gravida VI, para I, who had had five consecutive abortions. The pregnancy terminated at 25 weeks with severe chorioamnionitis. The umbilical cord had

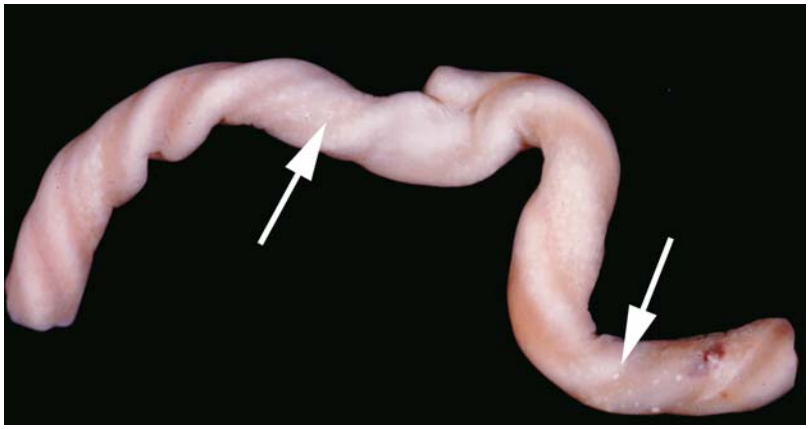

FIGURE 20.41. Umbilical cord from a patient with congenital candidiasis at 25 weeks' gestation. Note the numerous small, white plaques (arrows), representing abscesses ("granulomas"). Gravida VI, para I, abortus V.

numerous tiny plaques of white-yellow color. Histologically, these nodules consisted of infiltrates with acute inflammatory cells underneath areas of epithelial necrosis (Fig. 20.42). When one scrapes these small lesions and stains with periodic acid-Schiff (PAS) or silver methods, fungi are immediately recognized (Fig. 20.43). Hematoxylin an eosin (H&E) stains, on the other hand, hide the hyphae effectively. But fungal hyphae are also readily demonstrated with silver stains when they may be very difficult to identify in H&E preparations. Touch preparations from scraping cord lesions are diagnostic and thus helpful for neonatal therapy. Relative to the severity of the chorioamnionitis, the funisitis is generally only slight and it is often remarkably focal. The umbilical cord finding of surface granules with inflammatory cells and fungi is characteristic of congenital candidiasis. Although *C. albicans* is the most common candidal organism, infection with *C. parapsilosis*, a common skin inhabitant, has also been reported (Kellogg et al., 1974). We have seen two cases of infection with *C. tropicalis*, and Nichols et al. (1995), who also reviewed the sparse literature, described a 25-week premature with this infection. The fetus had massive pneumonia and there was marked chorioamnionitis but no funisitis. The mother had an IUD in place. Other than for the lack of hyphae, the histologic findings of our case were generally similar (Fig. 20.44). In an immunosuppressed (bone marrow transplant) patient with diamnionic/dichorionic (DiDi) twins, vaginal bleeding led to amniocentesis and recovery of budding yeast, *Candida lusitaniae*. Three weeks' of amphotericin therapy

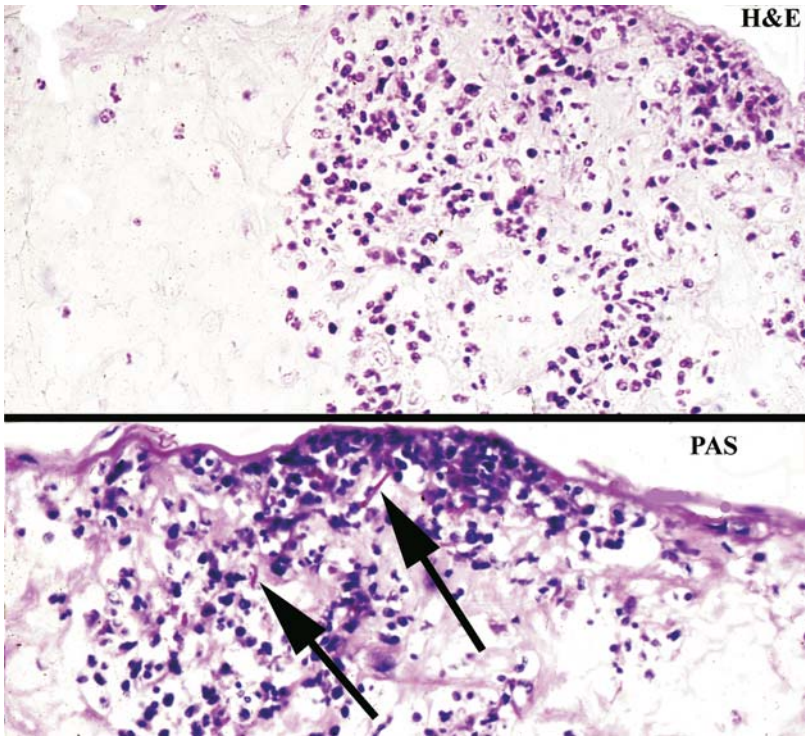

FIGURE 20.42. Candidiasis of umbilical cord. The lesions shown in Figure 20.41 are accumulations of inflammatory cells, debris, and hyphal organisms (arrows in PAS stain) of *Candida albicans*. Epithelial necrosis is striking at top H&E ×60 (top); ×240 (bottom).

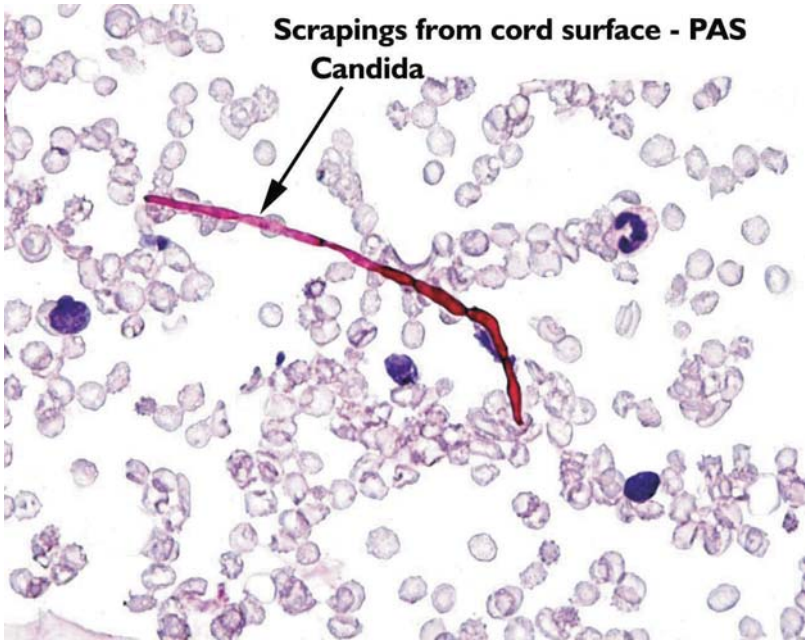

FIGURE 20.43. Scraping from one of the cord's surface nodules, stained with periodic acid-Schiff (PAS). Candidal organism at arrow.

apparently resolved the chorioamnionitis, although the placenta was not described (DiLorenzo et al., 1997).

A remarkable feature of congenital candidiasis is the frequency of its occurrence with unruptured membranes. We had postulated a silent, healed rupture in our original report. Our subsequent experience was that the organisms may readily penetrate the intact membranes. Why the placental infection is so uncommon, in comparison with the frequency of the vaginal infection, is unknown. It had been speculated that it results from fetal immunodeficiency, but findings of good plasma cell response to the congenital pulmonary infection negates this hypothesis (Hood et al., 1985). More likely is the efficiency of the endocervical mucus plug in preventing ascension. Neonatal candidiasis may be widespread, with skin rash, dark red skin appearance, pneumonia (Emanuel et al., 1962), meningitis (Levin et al., 1978), sepsis, and frequent intestinal contamination (Taschdjan & Kozinn, 1957). It may cause death but has also been treated successfully on several occasions. Abortions have also been due to *Candida* infection (Buchanan & Sworn, 1979; Smith et al., 1988). We have seen elevations of neonatal WBC counts to 80,000 in congenital infection of a premature infant. There had been rupture of membranes for 3 days.

A well-studied case showed convincing evidence of antenatal septicemia (Bittencourt et al., 1984). In this case, a large fungal invasion into an umbilical vein was shown; moreover, there were many fetal and villous candidal lesions. The latter showed focal necrosis, chronic villitis, and intervillous abscesses. Congenital infection

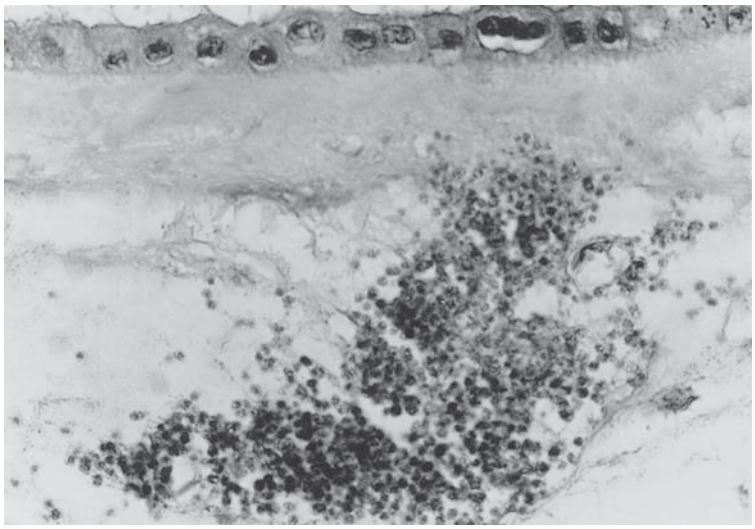

FIGURE 20.44. Subamnionic cluster of *Candida parapsilosis* in an infant with cutaneous congenital candidiasis (blisters) after prolonged rupture of membranes. The infant did well. Note the absence of hyphae and the intact amnionic epithelium. At other sites, chorioamnionitis was prominent. H&E ×600.

has been associated with a retained IUD on several occasions (Schweid & Hopkins, 1968; Ho & Aterman, 1970; Bittencourt et al., 1984; Spaun & Klünder, 1986; Smith et al., 1988; Elliott, 1989; Qureshi et al., 1998). Delaplane et al. (1983) believed that, in their case, the fungus may have been introduced by amniocentesis. Whyte et al. (1982) suggested that at least 30 cases had been reported, and they added 18 of their own. At least 10 additional cases can be added to this list, bringing the total to well over 50 congenital candidal infections, and Pradeepkumar et al. (1998) added five additional typical cases. Bader (1966) reported its occurrence in an anencephalus and depicted the extent of placental involvement. Rhatigan (1968) and Franciosi and Jarzynski (1970) each added a case. Nagata et al. (1981) described a fatal case of pulmonary mycosis and cited some cases from the Japanese literature. Johnson et al. (1981a) reported two cases and gave suggestions for therapy. Delprado et al. (1982) provided excellent illustrations in their report of three cases. They highlighted the association with unruptured membranes and a retained IUD. Shalev et al. (1994) delivered amphotericin transcervically when fungi were cultured from amniocentesis fluid. Rode et al. (2000) also administered amphotericin when, in serial amniocenteses for unexplained hydramnios, the organism was demonstrated and cultured. The neonate died from disseminated infection and the placenta was characteristic. Pera and associates (2002) deduced from chart review that neonatal candidiasis (*C. albicans* and *C. parapsilosis*) was more common in women receiving antibiotics and dexamethasone in pregnancy.

The case report by Levin et al. (1978) is of particular interest. It involved a set of DiMo twins delivered vaginally at approximately 30 weeks' gestation. The mother was febrile. The amniotomy of twin A resulted in meconium-stained fluid, but this infant did not have fungal infection at autopsy. Twin B, whose membranes had ruptured 9 days prior to delivery and whose amnionic sac was found to be dry at delivery, had cerebral candidiasis. In the placenta, a focus of candidal hyphae was found near the insertion of the umbilical cord from twin B, and chorioamnionitis was more severe.

A case of *Torulopsis (Candida) glabrata* infection of placenta and fetus in a patient with sickle cell anemia, was illustrated by Sander et al. (1983). They assumed that the maternal immune compromise may have rendered this infection more possible. The only previously described case was in a patient with a retained IUD. This widely distributed yeast has now been placed in the *Candida* genus; it lacks hyphae. In the two reported cases there was chorioamnionitis, but the umbilical cords had no lesions. In Sander's case, the patient had cerclage for repeated abortions; the stillborn twins had a fungal aspiration pneumonia. Infection had occurred before rupture of membranes, and marked deciduitis was present. The most remarkable feature of the lesion in the umbilical cord are the peripheral nodules with invading fungi. These nodules contain fungi but are compressed Wharton's jelly, perhaps from digestion of the mucopolysaccharides by the yeast. Few WBC are present in these nodules. Other comprehensive reviews are those by Johnson et al. (1981a), Gerberding et al. (1989), and Schwartz and Reef (1990).

Approximately 65 pregnant patients with **coccidioidomycosis** had been reported when VanBergen et al. (1976) reported a fatal case. The placenta had numerous infarcts with spherules of *Coccidioides immitis*, accompanied by inflammation, necrosis, and fibrin deposits. Figure 20.45 shows a cross section of a placenta with coccidioidomycosis. Figure 20.46 is a representative microscopic appearance of the lesions and the organisms. An acute inflammatory response around the fungal spherules is common, as is extensive fibrin deposition. Smale and Waechter (1970), in an analysis of 15 cases with disseminated infection, mentioned three with placental involvement and one presumed fetal infection. Most commonly, the organism remains confined to the placenta, where it produces infarctive necroses. This picture was first described by Vaughan and Ramirez (1951), who saw 33 cases of coccidioidomycosis complicating pregnancy.

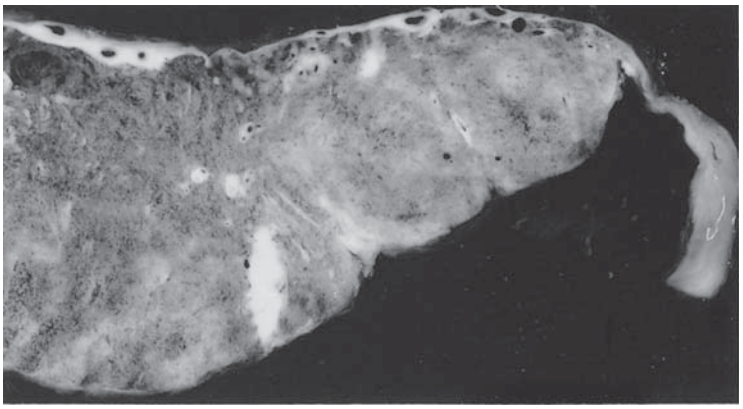

FIGURE 20.45. Section of mature placenta from a mother with coccidioidal meningitis. The coccidioidomycosis lesions are the white infarct and the punctate fibrin deposits. The mother was treated with amphotericin B. The neonate was normal.

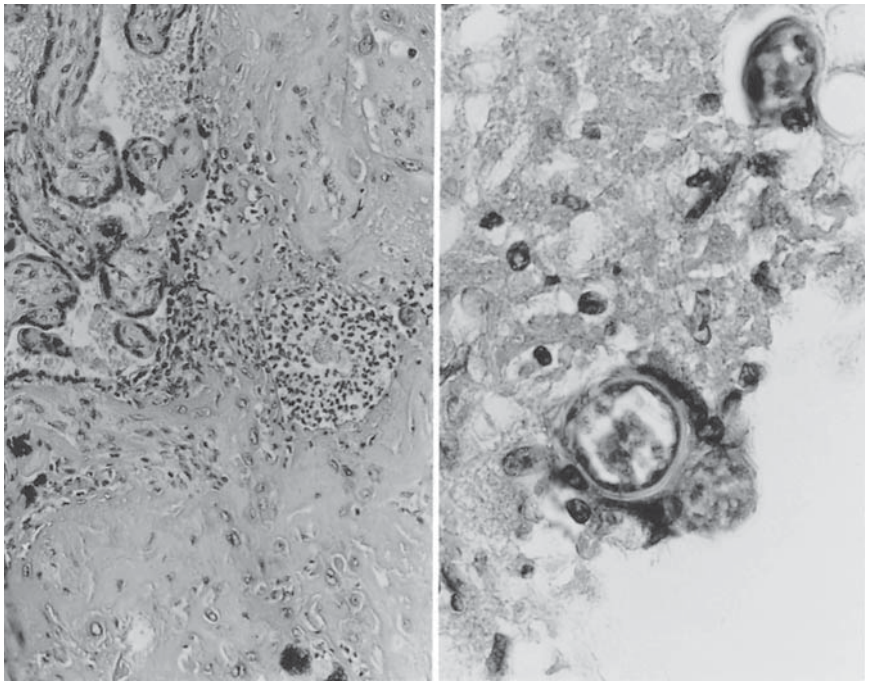

FIGURE 20.46. Microscopic view of coccidioidomycosis of the placenta (case in Fig. 20.45). Left: Note the spherule in the X-cell deposit with fibrin and an acute inflammatory reaction. Right: Several large spherules are engulfed in macrophages (right). H&E ×250 (left); ×640 (right).

Only one had lesions in the placenta. They were infarctive, necrotic lesions with "purulent filled centers, full of spherules." The premature infant delivered to that mother died at the age of 6 months but was free of the disease. The other infants also did not contract the infection transplacentally. Shafai (1978) described disseminated infection in a set of premature twins whose mother died soon after giving birth. They found no lesions in the placenta but still assumed that transplacental infection must have occurred. Bernstein et al. (1981) described another presumptive congenital infection, but they did not describe the placenta. Spark (1981) has critically reviewed all cases of congenital coccidioidomycosis and came to the conclusion that transplacental dissemination was unlikely for any of them. The mode of neonatal infection, he believed, was inhalation of infected material ("decidua") during delivery.

We have seen massive placental involvement with *Coccidioides* lesions unaccompanied by neonatal illness (McCaffree et al., 1978). In one patient in whom the disease was treated with amphotericin B during the entire gestation, the fetus was normal and the placenta merely showed old infarcts and fibrin deposits, without stainable organisms. Peterson et al. (1989) also described a patient with coccidioidal meningitis treated with amphotericin during two pregnancies in whose placentas there were no organisms. Walker et al. (1992) described maternal reactivation of coccidioidomycosis in pregnancy, positive neonatal cord titers, but a negative placenta. A pregnant patient with lymphadenopathy due to *Paracoccidioides brasiliensis* was described by Slevogt et al. (2004). The patient was treated successfully and a healthy infant was born.

Cryptococcosis of the placenta was found by Kida et al. (1989) in a patient with acquired immunodeficiency syndrome (AIDS). It had not invaded villi, and the infant did not develop lesions. The mother developed widespread cryptococcosis. Through the courtesy of Dr. G. Altshuler, we examined placental sections with cryptococcal abscesses of a patient with systemic lupus erythematosus (SLE). She suffered cryptococcal meningitis, presumably because of steroid therapy for SLE. In the intervillous spaces of the immature placenta there were large colonies of cryptococcal organisms; inflammation was scant and no invasion of the villi was found. The neonate (850 g) died and had no evidence of disease (Molnar-Nadasdy et al., 1994). We have also seen the slides of a patient who had been treated with ketoconazole for pulmonary **blastomycosis** 4 years earlier (Dr. E.G. Chadwick, Chicago, personal communication). The patient had been free of apparent disease but was initially infertile. A healthy term infant was eventually delivered. The placenta then appeared grossly peculiar as it had a nodular consistency, and numerous granulomas as well as chronic villitis at the maternal floor. Organisms were not identified. It remains unknown whether the lesions were due to endometrial blastomycosis or whether this is merely a case of villitis of unknown etiology (VUE).

Virus Infections and Villitides

Cytomegalovirus Infection

Congenital cytomegalovirus (CMV) infection is a common disease. Yow (1989) stated that 3000 to 4000 infants are born in the United States each year with

symptomatic disease, and a large number of children suffer late-onset manifestations of the infection, including hearing loss, blindness, and retardation. Stagno et al. (1986) found that 1.6% of seronegative women of high-income groups converted CMV titers during pregnancy, whereas 3.7% of low-income group women did so. The writer of an editorial (Anonymous, 1989c) has found that the rate of transmission to the fetus after recent maternal infection is between 20% and 50%. Moreover, infection during the first half of pregnancy is more destructive to the fetus and it has now been found that infants also infected with HIV have a greater propensity to suffer CMV infection (Doyle et al., 1996). Symptomatic fetal infection can also occur from an immune mother when a new strain of virus is acquired (Boppana et al., 2001). Nigro et al. (1999) found discordant expression of CMV infection in dizygotic twins (one had hydropic change), and that the edema disappeared when the fetus was treated with hyperimmune globulin.

It is also now recognized that the virus is often acquired by sexual contact (Chretien et al., 1977). The widespread nature of this infection was first appreciated by Weller (1971), who had emphasized its protean clinical manifestations. Many virus infections are accompanied by severe inflammation of the placental villi ("villitis"). An excellent review of these lesions is found in the contribution by Altshuler and Russell (1975). Schwartz and his colleagues (1992) have characterized the inflammatory response in this villous infection. They found marked "hyperplasia of fetal-derived placental macrophages . . . lymphocytic villitis . . . characterized by positive staining with T-cell antibodies." Plasma cells staining for immunoglobulin G (IgG) and IgM secretion were present in the second trimester, but no IgA positivity was found. Van den Veyver et al. (1998) showed that the virus is readily identified in amnionic fluid, blood, pleural fluid, and tissues by employing PCR and showed a high frequency in samples of high-risk infants.

Infection with CMV is a major cause of chronic villitis. The fetal and neonatal disease has many manifestations, ranging from hydrops fetalis (Quagliarello et al., 1978; Fadel & Riedrich, 1988; Mazeron et al., 1994), obstructive uropathy (Symonds & Driscoll, 1974), meconium peritonitis (Pletcher et al., 1991), macerated stillbirth, and cerebral palsy, to minimal hearing loss (Saigal et al., 1982b) or severe CNS destruction (Schimmel et al., 2001). Moreover, some of these manifestations may be ascertained only years later (R.F. Pass et al., 1980; Williamson et al., 1982, 1990). Details of congenital CMV infection have been reported on many occasions (Embil et al., 1970; Krech et al., 1971). A very typical case of intrauterine CMV infection was described in detail as a Cabot case (Modlin et al., 2003).

Ahlfors and colleagues (1988) reviewed the literature of the infection in twins and reported two of their own cases that were discordant for manifestations of CMV infection. They postulated that monochorionic MZ twins were more likely to be concordant for CMV infection, but lamented that the information on placental and genetic status is too often missing from case reports to draw definitive conclusions. It was their suggestion that fetal (as well as maternal) immunologic response may be of importance in the expression of the prenatally acquired infection. They ruled out, from knowing the location of the twin placentas, that a CMV endocervicitis caused ascending fetal infection.

Congenital infection is perhaps also occasionally acquired from infected endometrium. The presence of CMV in endometrial glands was demonstrated in five of 59 spontaneous abortions by Dehner and Askin (1975). The CMV inclusions have also been found in endocervix (Wenckebach & Curry, 1976). The virus has often been cultured from seminal fluid (Lang & Kummer, 1972) and from amnionic fluid (Weiner and Grose, 1990). Stagno et al. (1982) showed that fetal infection is more serious when it occurs during a primary maternal infection than when it follows recurrent maternal disease. These cases are reasons to consider the benefit of a vaccine (Medearis, 1982). Neonates with this infection may excrete virus for years. They thus become a major source for infection of pregnant mothers and toddlers in day-care centers (Pass et al., 1987). In twin pregnancies, CMV infections have been seen in both twins (Saigal et al., 1982a) but occasionally also in only one twin (Eachempati & Woods, 1976; Stagno et al., 1982).

Fetal intracranial calcifications have been seen sonographically (Ghidini et al., 1989), and neonatal perivascular echogenic signals were demonstrated in their basal ganglia (Teele et al., 1988); the involvement of vessels is a hallmark of this infection. It has been suggested that it may be the cause of cerebral microgyria and other lesions (Dias et al., 1984). Other sonographic manifestations have been transient hydrops (Mazeron et al., 1994), abnormal triple-screen results and hyperechoic bowl (Peters et al., 1995), hydrocephaly, and growth retardation (Lipitz et al., 1997). Viral isolates can be obtained from amnionic fluid and fetal blood samples (Hagay et al., 1996). The virus may also be identified serologically, by immunofluorescence, PCR of DNA samples, or in situ hybridization (Ozono et al., 1997).

Fetal infection is undoubtedly most often acquired during primary maternal infection from maternal viremia and by the passage of virions through the destroyed trophoblast. This ability of CMV to infect and destroy the trophoblast has been shown in placental explants by Amirhessami-Aghili et al. (1987), and Chan et al. (2002) found this damage to be mediated by TNF-α. Interestingly, Pizzato et al. (2003) found by in vitro infection of cells that CMV infection downregulates the human leukocyte antigen (HLA)-G_1 expression. Despite this placental infection, no uniform **macroscopic** findings can identify CMV infection of the placenta; thus the selection

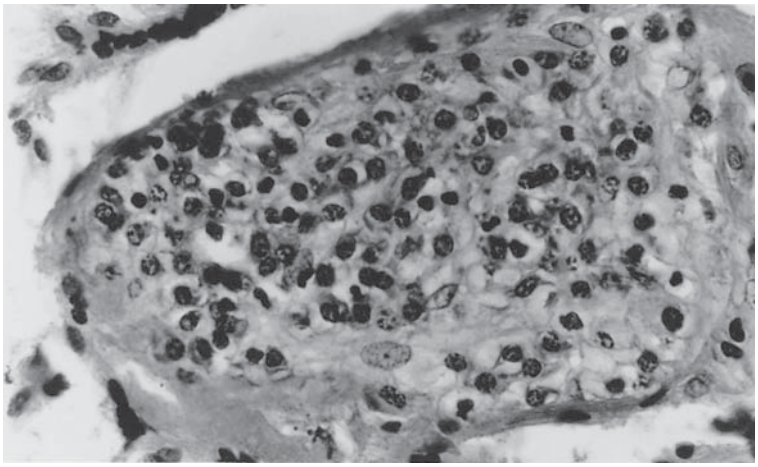

FIGURE 20.47. Congenital cytomegalovirus infection. Marked chronic villitis, composed almost entirely of plasma cells, is evident, as is focal necrosis of the trophoblast and capillary walls. The specimen is from a term gestation, and the mother reportedly had porphyria. H&E ×650.

of histologic material is difficult, although surface vessels are at times thrombosed and should arouse suspicion (Fig. 20.47). Small placentas with growth-restricted fetuses are common and thromboses may exist. A significant problem in understanding this infection is that some known prenatal infections (positive culture from amniotic fluid) may be followed by normal outcome (Weiner & Grose, 1990). We have also seen many cases of unsuspected CMV infection histologically when the placenta was sectioned for other reasons. For instance, in one case of maternal porphyria, typical CMV inclusions were found in the placenta and the neonate had hepatitis. The maternal disease was a manifestation of a primary infection with this virus and was misinterpreted as porphyria. In another case of a spontaneous abortus at 15 weeks' gestation with an unremarkable macerated fetus, there were widespread cytomegalic cells in the lung, spleen, skeletal muscle, and placenta. The mother had only had a minor "sore throat" 1 week prior. Remarkably, the placenta had extensive destructive villitis. Ultimately, either the virus has to be cultured, or inclusion body cells have to be identified. Although the classical histologic features are not mistakable, they are often so widely scattered through the villous tissue that only extreme scrutiny of many sections allows the diagnosis from placental sections.

The **histologic** hallmark of CMV infection in the placenta are chronic lymphoplasmacytic villitis (Fig. 20.48), thrombosis of villous capillaries often with adjacent hemosiderin deposits, necrosis of villous tissue and trophoblast (Fig. 20.49), fibrosis of villous stroma (Fig. 20.50), and inclusion-bearing cytomegalic cells (Fig. 20.51). The inclusion bodies may be characteristic nuclear "owl-eye" cells, but are often also of cytoplasmic nature. They are commonly seen in villous capillary endothelium but are also found in the stromal cells of villi. Garcia et al. (1989), who provided an excellent study of placental changes in CMV infection, found owl-eye cells in decidua and amnion as well. They employed the fluorescent antibody technique for diagnosis (see also McCaffree & Altshuler, 1979) and suggested that some types of gross morphologic abnormalities are frequent. Mostoufi-Zadeh et al. (1984) depicted owl-eye cells in the epithelium of the umbilical cord. Saito et al. (1977) described an abortion

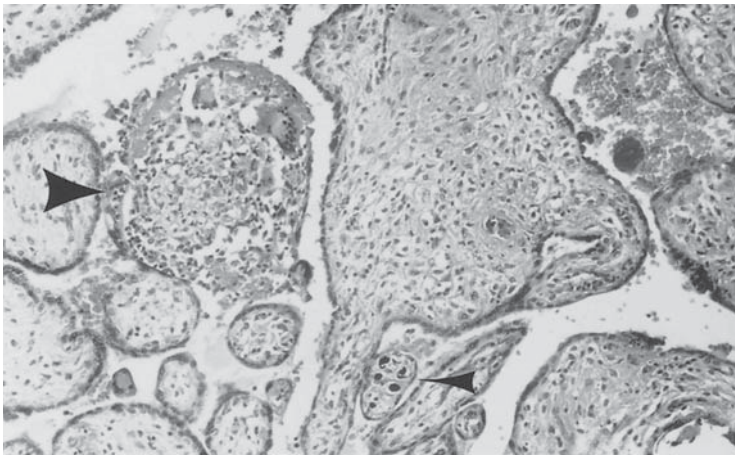

FIGURE 20.48. Destructive villitis (large arrowhead) in congenital cytomegalovirus (CMV) infection. Inclusion bodies, or owl-eye cells (small arrowhead), are also present in this 14 weeks' gestation. H&E ×150.

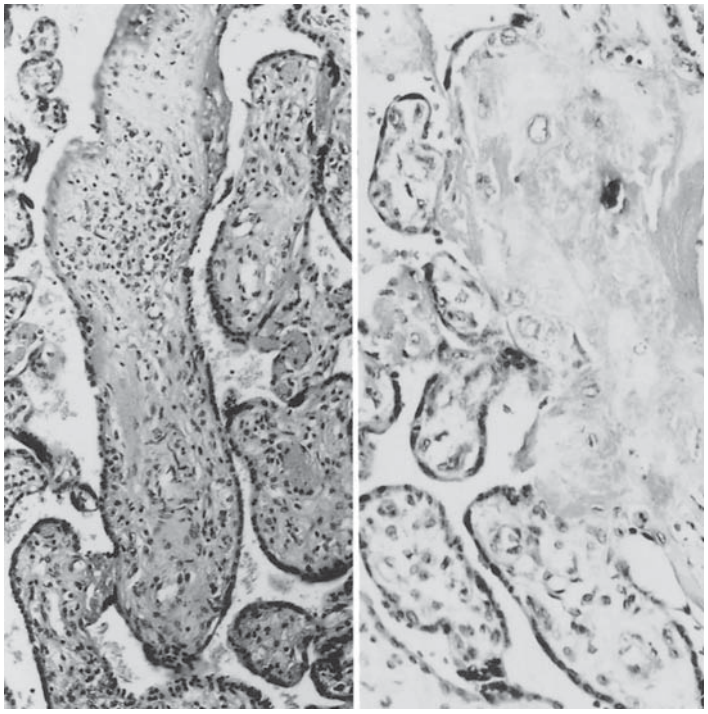

FIGURE 20.49. Evolution of fibrosis of the villi with a CMV infection. Left: A villus has plasma cell infiltration, trophoblast necrosis, vascular obliteration, and early fibrosis. Right: A completely hyalinized villus contains a focus of calcification and hemosiderin but no trace of CMV infection. H&E ×160 (left); ×260 (right).

with a large number of villous inclusion bodies typical of CMV infection. They diagnosed it as herpes simplex infection, however. We believe they made an incorrect diagnosis caused by an error in the interpretation of the serologic results. The CMV titers were also rising. Their analysis included an excellent electron microscopic demonstration of the virus packets, typical of a herpes-type virus (see also Donnellan et al., 1966, for electron microscopy). Vasculitis of chorionic vessels (Fig. 20.52) may lead to thrombosis and calcification. Huikeshoven et al. (1982) as well as Grose and Weiner (1990) made the diagnosis of CMV infection by recovering the virus from amnionic fluid at amniocentesis, undoubtedly because of fetal renal involvement. The placental and neonatal features in the former study were typical of CMV infection. The virus can now be detected in histologic sections by in situ hybridization (Wolber & Lloyd, 1989). Sachdev et al. (1990) have used the hybridization technique to identify CMV infection in cases of chronic villitis. They found typical inclusions in three of eight cases of villitis and were able to diagnose three additional cases of CMV infection because of this technique. Mühlemann and her colleagues (1992) have provided an excellent immunocytochemical study of six CMV-infected placentas. They suggested that histologic features are often inconclusive in this congenital infection and found inclusion bodies in

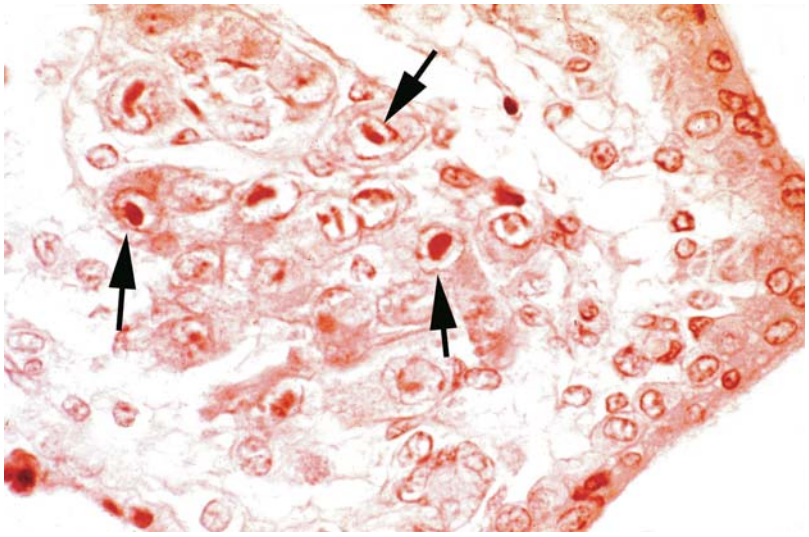

FIGURE 20.50. Owl-eye nuclei (arrows) of a cytomegalic cells in a villus of a patient with CMV placentitis. This cell also contains many cytoplasmic virus particles. H&E ×650.

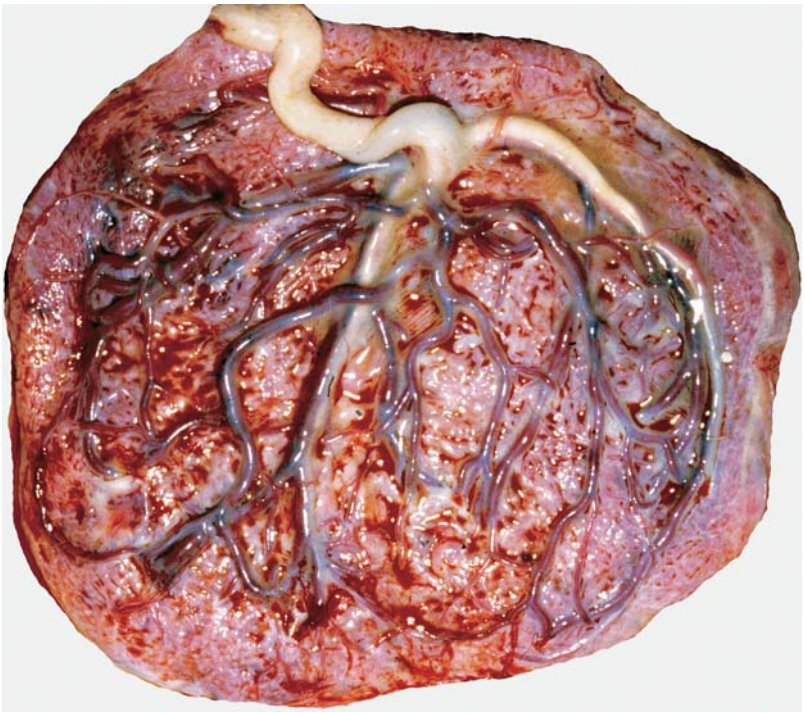

FIGURE 20.51. Term gestation of congenital CMV infection that led to calcified thrombosis of surface vessels (yellow streaks).

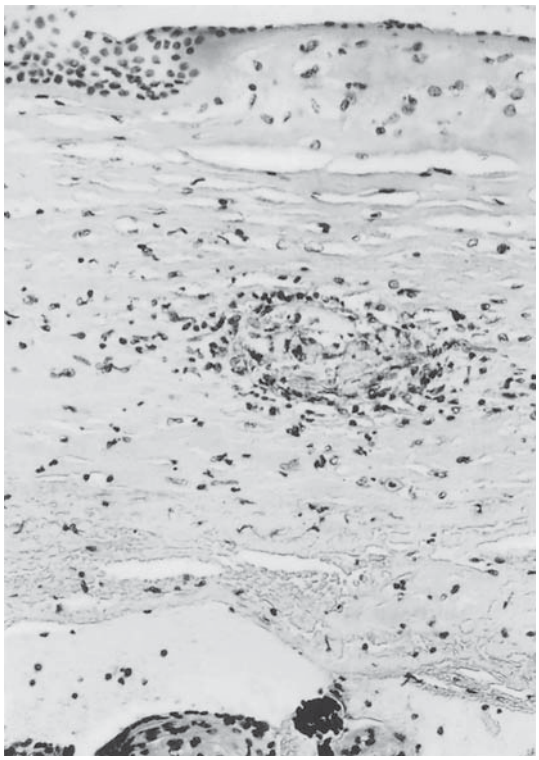

FIGURE 20.52. Chorionic vasculitis in a patient with CMV infection at term. There is more necrosis than inflammation. The placenta had marked chronic villitis. The fetus was stillborn. H&E ×160.

only one of six cases. Immunocytochemistry, on the other hand, revealed viral antigen in five of the six placentas. The antigen was found to be mostly in the villous stroma, once in the syncytiotrophoblast, and sometimes in endothelial cells as demonstrated by double-staining these cells. Kumazaki et al. (2002b) looked for CMV DNA in 254 placentas and correlated it with maternal serum status. Seronegative mothers had negative placentas; 30.5% of seropositive mothers' placenta had antigen in various locations.

The cellular response to this infection is characteristic. It is mononuclear; during the second half of gestation, it is typically accompanied by fetal plasma cells, but we have seen it as early as at 15 weeks' gestation in the placental villi. Here it is then a question of whether the plasma cells are of fetal or maternal origin. This question has not been satisfactorily answered as yet. Plasma cells are not expected to be produced by fetuses at 13 weeks' gestation. Hybridization studies with Y-chromosome probes in appropriate cases are indicated to rule out maternal B-cell immigration, an important consideration for the understanding of chronic VUE. Mostoufi-Zadeh et al. (1984) opined that the fetal infection is more severe when a plasmacellular, rather than a lymphocytic, response is found in the villi. The plasma cell infiltration and the cytomegalic cells in the placenta were first described by LePage and Schramm (1958) and subsequently by LeLong et al. (1960). Since then, there have been numerous observations substantiating and expanding on these findings (e.g., Rosenstein & Navarrete-Reyna, 1964; Monif & Dische, 1972). Blanc (1961b), in a

thorough review of the placenta of prenatal infections, described the villous necrosis; Quan and Strauss (1962) discussed the differential diagnosis of CMV infection from erythroblastosis.

The findings of many other authors are summarized in our previous review (Benirschke et al., 1974). In that paper we described five cases, one of which is of particular interest. It was a therapeutic abortion at approximately 15 weeks' gestation. The patient had fever of unknown origin and antibody titers to CMV and toxoplasma. A double infection was suspected, but no toxoplasmosis was found in the abortus. At dissection, no macroscopic lesions were seen but viral inclusions were found in many organs histologically (Fig. 20.53). There was only a sparse inflammatory response. The villous infection and focal thrombosis in pulmonary vessels were particularly striking. A case of presumed double infection was described by De Zegher et al. (1988), in which *Toxoplasma* was definitely identified, and saliva and urine cultures yielded CMV. The alleged double infection illustrated by Demian et al. (1973), however, was not correctly identified. Only CMV was shown, the cytoplasmic granules representing virus, not *Toxoplasma* as was presumed.

It has often been asked just when the first fetal plasma cell response to CMV can be seen. This question is not yet resolved, as previously stated. Altshuler and McAdams (1971) clearly identified plasma cell villitis at 19 weeks' gestation, but it may commence as early as at 10 weeks, judging from Altshuler's (1973a) second case, seen at 13 weeks' gestation (Fig. 20.54). The owl-eye inclusions are characteristic of CMV infection, and the diagnosis can be made confidently on that basis alone. When only enlarged cells with cytoplasmic inclusions are present, however, the diagnosis of CMV infection is less secure. Serologic studies, virus isolation, and modern techniques of demonstrating the viral genome by hybridization are then needed. When different strains of the virus were thus identified with endonuclease cleavage of viral DNA, "no common pattern could be associated with these eight strains (of congenitally acquired virus) in comparison with strains from postnatally infected children" (Grillner et al., 1987). Borisch et al. (1988) successfully identified the antigen in the nucleus and cytoplasm by in situ hybrid-

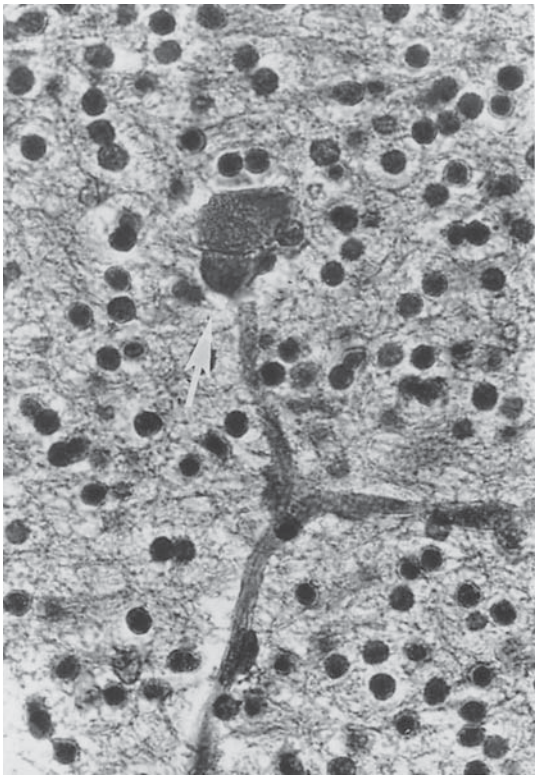

FIGURE 20.53. Fetal brain at 15 weeks' gestation with a CMV cell at the terminus of the capillary. There is no inflammation or destruction. Placenta had numerous CMV cells. H&E ×150. (*Source:* Benirschke et al., 1974, with permission.)

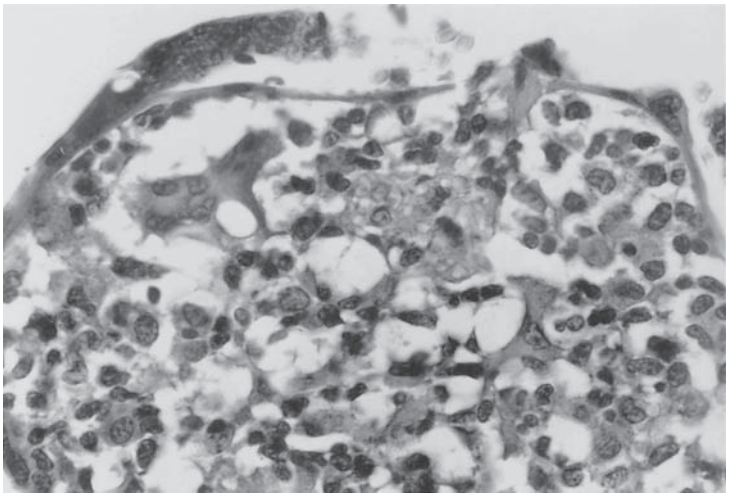

FIGURE 20.54. Cytomegalovirus infection of the placenta at 13 weeks' gestation, with plasma cell infiltration, edema, and trophoblast necrosis. H&E ×520. (Courtesy of Dr. G. Altshuler, Oklahoma City, Oklahoma.)

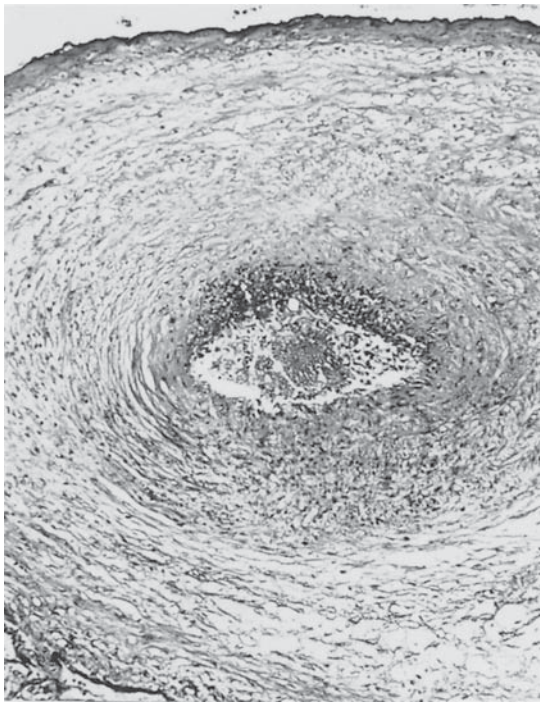

FIGURE 20.55. Chorionic vasculitis, necrosis, and early thrombosis with a congenital infection, presumably CMV, at 20 weeks' gestation. Outcome was a stillborn fetus. See Figure 20.56. H&E ×100.

ization, and Chehab et al. (1989) were able to do so with PCR of the DNA obtained from paraffin-embedded tissues. One can only hope that in the future the nature of such placental lesions, as depicted in Figures 20.55 and 20.56 will be resolved by these methods.

Herpes Simplex Virus Infection

Transplacental infection with herpes simplex virus (HSV) does occasionally occur. It is more serious for the fetus when primary, rather than recurrent, herpes virus infection occurs during pregnancy (Brown et al., 1987). But transplacental infection is uncommon, presumably because of the protective nature of transplacentally acquired maternal antibodies; most women become immune to HSV before reaching childbearing age (Nahmias et al., 1970). "The major problem in newborn infection then is one of natal transmission of HVH (*Herpesvirus hominis*) through recurrent type 2 infections of the maternal genital tract" (Alford et al., 1975). Why it is that fatal infections occur sometimes in utero, and not at other times, and what the reason is for recurrent and latent infections remain unresolved questions. Ideas about the latency of HSV were discussed in an editorial (Anonymous, 1989b), and a succinct review of the fetal infection with HSV has been provided by Baldwin and Whitley (1990). Johnson et al. (1989) found in a survey of 4201 serum samples that 16.4% of the U.S. population from 15 to 74 years of age was infected with HSV-2.

Herpes virus is silently shed by 2.3% of pregnant women (Wittek et al., 1984), although lower numbers (0.1–0.4%) have also been cited (Witlin et al., 1998). Yen et al. (1965) succinctly described and depicted the cervical and vaginal lesions of herpes virus infection and presented three infants with symptomatic mothers. Two newborns had an apparently congenital infection. Kell et al. (2000) suggested that neonates with disseminated herpes infection have acquired it in utero in 4%, natally in 86%, and postnatally in 10%; thus, prenatal infection

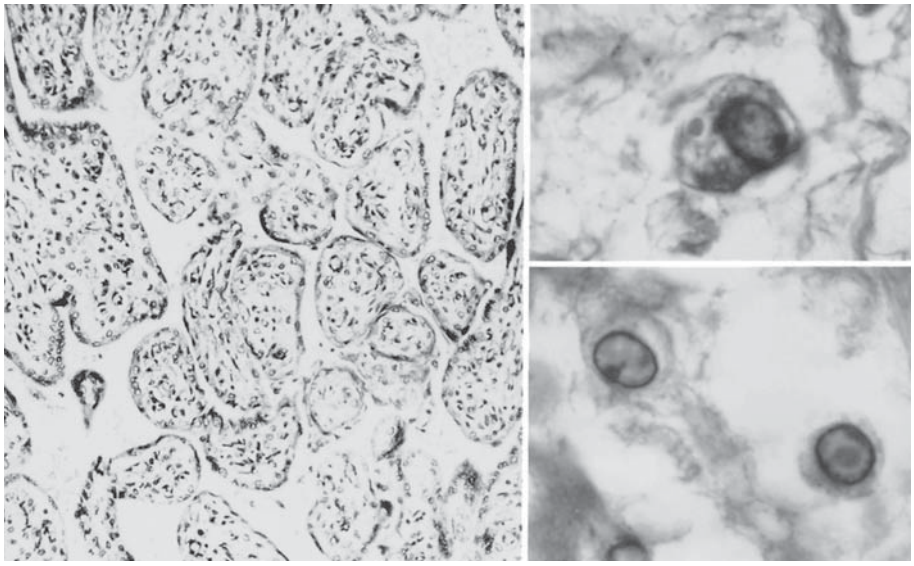

FIGURE 20.56. Same case as in Figure 20.55. Chronic villitis (left) with enlarged cells having some of the qualities of CMV cells. The inclusions are not typical, however. H&E ×160 (left); ×1600 (right).

is uncommon. In fact, it has led to intrauterine demise, as in the case described by Barefoot et al. (2002) with extensive facial necrosis demonstrates. Herpes virus has also been detected before delivery (of a healthy child) from aspirated amnionic fluid (Zervoudakis et al., 1980). Herpetic endometritis has been demonstrated with and without an IUD (Abraham, 1978; Schneider et al., 1982), and Altshuler (1974) presented evidence for prenatal infection with an involved placenta (vide infra). Another case of presumed ascending infection was presented by Hain et al. (1980). They described the premature birth of a 590-g infant with a rash; there was necrosis in various organs at autopsy. The placenta showed cloudy membranes due to "extensive necrosis of amnion without inflammation." Necrotic areas were also present in chorion, and a lymphoplasmacellular infiltration was evident, as in Altshuler's case. In their case, however, chorionic vessel thrombosis and many inclusion bodies as well as "ground-glass" nuclei were present. The mother had primary herpetic vulvitis 4 weeks before delivery. Hyde and Giacoia (1993) have described an important case of severe, destructive congenital HSV infection, delivered by cesarean section of a cervically infected patient. At those portions of the intact membranes that were closest to the cervix, they found immunologically HSV-positive cells in the subamnionic connective tissue, aside from a mild chronic funisitis. This case strongly supports an ascending infection, occurring even with intact membranes. Peng et al. (1996) also described a serious prenatal infection of a twin fetus, whose twin became infected with scalp lesion resulting after amniotomy for scalp electrode placement. Brown et al. (1997) found that when HSV is acquired during pregnancy near the time of delivery, congenital infection may be a sequel. Postpartum endometritis may also be a consequence of HSV infection (Hollier et al., 1997). Witlin et al. (1998) found only focal villous edema and sclerosis in the placenta of a clearly in utero infection.

The review of Baldwin and Whitley (1990) summarized 71 cases of presumed prenatal herpes virus infection. Many of these cases were not fully studied, and the placentas were examined in only a few. The early reports of fetal infection by Mitchell and McCall (1963), Zavoral et al. (1970), Torphy et al. (1970), and Monif et al. (1985) had no placental study. Witzleben and Driscoll (1965) were the first investigators to describe the placental changes in proved congenital herpes simplex infection, and they reviewed other fatal cases of neonatal herpes infections. The mother in their case suffered a primary disseminated infection 1 month before delivery. The neonate remained well until day 6 and then died from generalized disease. The placenta was grossly unremarkable but had many areas of villous necrosis. It included trophoblast and stroma. An inflammatory reaction was absent, but inclusions were found in the placenta and fetus. Nakamura et al. (1985) demonstrated immunologic staining and, by electron microscopy, typical herpes particles in stromal cells of villi in a presumably hematogenously transplacental infection. Other cases with prenatal onset are those by Chatterjee et al. (2001) with placentitis, and 15-week monochorionic twins and bland villous necroses (Bedolla & Stanek, 2004).

Other excellent descriptions of the placenta in herpetic infection came from Altshuler (1974, 1984), who summarized the earlier-mentioned case in the context of other placental inflammations. There were no complications in the term pregnancy he described, and no herpetic lesions had been known or noted. The infant developed blisters on day 4, with isolation of HVH. He was treated and discharged but continued having skin lesions. The meconium-stained placenta had many areas of necrotizing deciduitis and amnionitis; chorionic vasculitis and funisitis were attended by superficial amnion necrosis. The exudate contained leukocytic and extensive plasmacellular infiltrates (Fig. 20.57). The villous tissue was not altered, and inclusion bodies were absent, but the prenatal acquisition of the infection is evident from the unusual plasmacellular funisitis, not known in banal infections. S. Hyde (personal communication) has also seen a case of neonatal herpes infection with extensive chronic villitis. In contrast to the usual cases of VUE, however, many villi showed an extensive acute necrosis. He examined the lymphocyte markers in this case, finding that 1% of villous inflammatory cells were CD45 Ro (B cells) marked, but no staining occurred in the necrotic villi; many positive CD45 Ro (T cells) and CD68 markers (macrophages) were present in the affected villi and the chorionic plate.

The role of molecular pathology in the diagnosis of transplacental herpes infection was described by Schwartz and Caldwell (1991). They reported the delivery of a neonate who remained well from a patient with suspicious genital lesions. Previously, HSV had been confirmed by culture. Microscopic sections of the placenta were grossly and microscopically normal. In situ hybridization with a biotinylated DNA probe for HSV was counterstained. Subchorionic tissue (maternal-derived tissue of the decidua capsularis) stained positively for the antigen. It is our opinion that these findings are not specific for herpes antigen but that they reflect the biotin content that was so well later defined in endometrium by Yokoyama et al. (1993). These investigators were aware of the similarity of apparent inclusions in endometrium with those of herpes infection; they showed, however, that these vacuoles contained biotin. Thus, extreme care should be exercised in the interpretation of such immunologic localizations employing biotinylated probes in the immunologic reaction.

Bendon et al. (1987) emphasized deciduitis associated with their two cases of intrauterine HVH infection. One

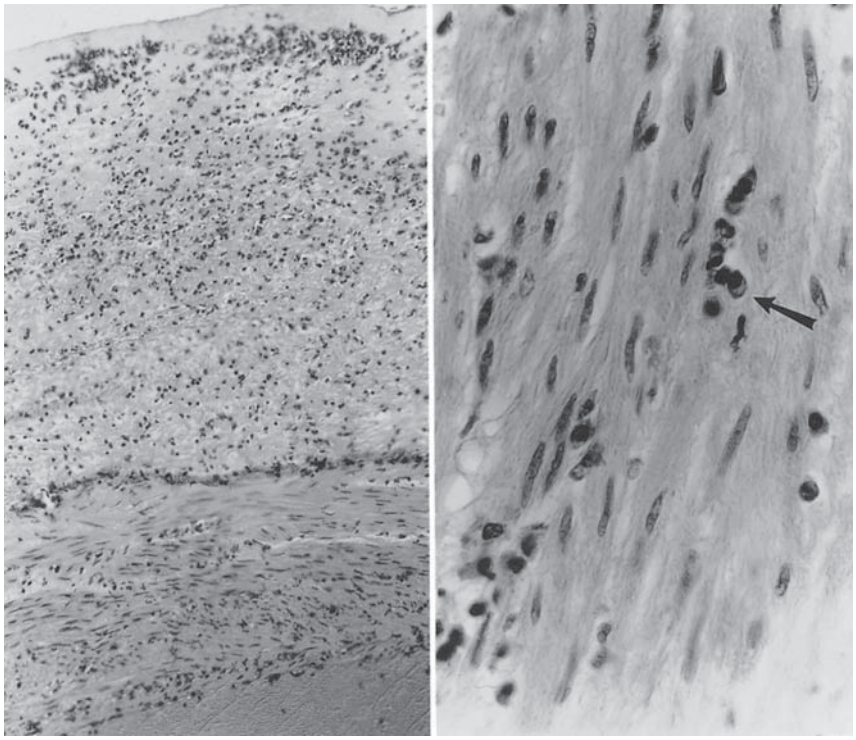

FIGURE 20.57. Congenital herpes virus infection of placenta. Note necrosis of the amnion, thickening of membranes, and intense plasma cell (arrow) infiltration. H&E ×160 (left); ×640 (right). (Courtesy of Dr. G. Altshuler, Oklahoma City, Oklahoma.)

was a stillborn 300-g abortus with macular skin lesions, and the other was a 3200-g neonate with blisters who was treated and survived. The authors were unable to detect antigen in cord or amnionic sac, by immunohistochemical reaction but found it at the decidual base of the placentas. For this reason, they suggested that infection may have been disseminated via neural fibers or through endometrial channels, rather than in an ascending manner. Berger et al. (1986) described a mother with herpetic encephalitis during pregnancy; a meconium-stained placenta and fetal infection occurred, despite acyclovir therapy. Gagnon (1968) recovered virus from the placenta but did not describe the organ. Dublin and Merten (1977) showed the severe cerebral necroses that occurred in discordantly affected DiMo twins at 29 weeks' gestation. They stated that the placenta was affected with hemorrhagic and fibrotic changes.

The differences in severity and types of placental and fetal reactions in prenatal herpes infection suggest that transplacental and ascending infection may both occur. Boué and Loffredo (1970) isolated herpes virus type 2 from abortion material and suggested that this infection may play a causal role in abortion. Naib et al. (1970) studied the outcome of pregnancy in women with herpes infection. When infection occurred during the first 4 months of pregnancy, abortions occurred significantly more frequently, suggesting a causal relation.

Two cases with undisputed congenital herpes infection have been seen by us. One was a stillborn without maternal illness or herpetic lesions. The placenta had necrotizing chorioamnionitis with true blisters (Figs. 20.58 and 20.59). Plasma cells were the most abundant cell type in the exudate. The unusual occurrence of plasma cells at this site cannot be overemphasized. The other case was

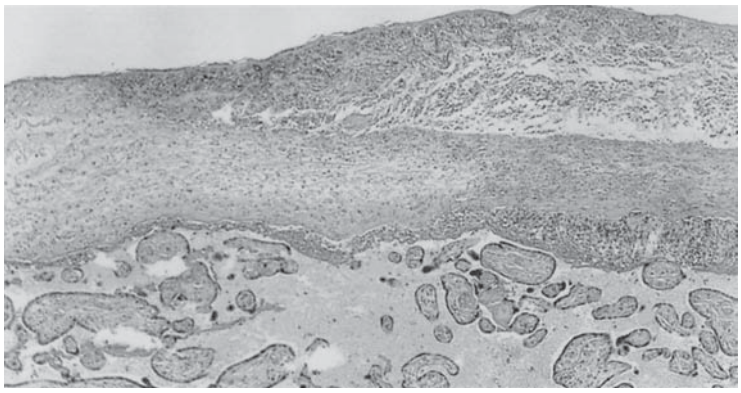

FIGURE 20.58. Congenital herpes simplex virus-2 (HSV-2) infection with stillbirth outcome. Note the subamnionic blister filled with plasma cells. Also present are chorionitis and amnion necrosis. H&E ×64.

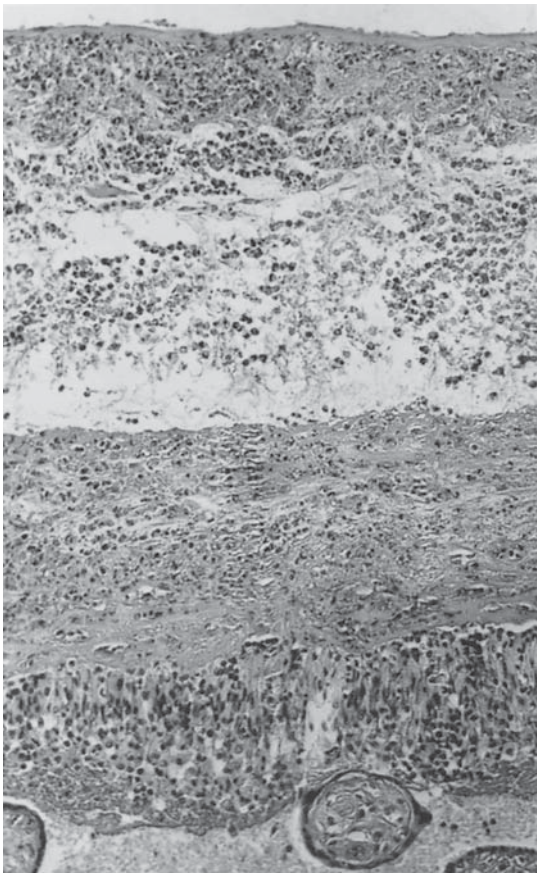

FIGURE 20.59. Congenital HSV-2 infection (same case as Fig. 20.58). The large collection of subamnionic plasma cells is unusual. H&E ×160.

reported by Herzen and Benirschke (1977). A cesarean section had been done for breech presentation; the membranes were intact. There was no maternal history of herpetic lesions, nor was the virus cultured from the mother. She had a titer of 1:32 that rose to 1:64 after birth, perhaps an insufficient criterion. The infant had severe disease and died. The placenta was circumvallate and had an unusually adherent amnion, and there were infarcts but no villitis. Inclusion bodies were found in the chorion. Severe plasma cell infiltration was present in the decidua; HSV-2 was isolated from fetal skin vesicles and the placental surface. Because of the absent villitis and the presence of chorioamnionitis, we speculated that it was an ascending infection. That opinion is supported by the absence of genital lesions in a large number of mothers with infected offspring.

This case raised further questions. In addition to the characteristic necrotic lesions found in neonatal herpes deaths (Hass, 1935), the autopsy findings included ocular, renal, and cerebral anomalies. The occasional association of congenital anomalies with HSV infection was discussed by Baldwin and Whitley (1989); some of these anomalies surely are the result of the virus infection. When this infant died at 21 days of age, he had massive destructive disease of the brain, resembling hydranencephaly. Virus recovery was attempted by culture and electron microscopy. Because of this failure and the proved HSV-2 disease, we searched for antigen by immunohistologic procedures (Robb et al., 1986a). Characteristic staining was found with this technique in a variety of tissues from this infant. We then studied abortion specimens and other conditions with unresolved etiology for the presence of herpes antigens. In some of these cases, herpes viral DNA could be detected by hybridization study. The brain and placenta of the neonatal death just discussed also had a strong staining reaction (Robb et al., 1986b). Although we are aware that this method cannot prove the existence of local residual HSV antigen, it is presumptive evidence for this correlation. In the placenta the antigen was prominently found in a subamnionic location, as were the herpetic lesions. Strong antigen reactivity was seen in other cases as well, such as in necrotizing funisitis and many cases of "maternal floor infarction." Future studies must to be undertaken to interpret these findings. Finally, Altshuler (personal communication, 1992) sent us the placenta of a child with congenital herpes infection whose umbilical cord surface showed only extensive acellular necrosis, without any attending inflammatory response. Herman and Siegel (1994), who described another case of congenital HSV-2 infection, emphasized the many calcifications in the newborn's organs but did not discuss the placenta.

Varicella (Chickenpox)

Pregnancy complicated by chickenpox is fairly uncommon but it may have serious sequelae for fetus and mother (Katz et al., 1995). Despite the fact that most cases of adult chickenpox occur beyond the reproductive period (Stagno & Whitley, 1985), presumptive transplacental infection has been described several times. In a review of 18 maternal varicella pneumonias, Pickard (1968) noted that only three infants were without the disease; 38 neonatal cases of chickenpox had been described by then, with a 21% mortality. Sauerbrei and Wutzler (2000, 2001) review all of the clinical features and the length of incubation, and demonstrate the devastating nature of the illness when it is acquired in utero. Most interestingly, Bruder et al. (2000) observed a 33-week premature with anterior horn destruction, necrosis of one arm, and intestinal atresias that could be attributed to this viral infection. A chronic, necrotizing lesion was found in the placenta. Four other cases of major CNS lesions come from Mustonen et al. (2001) but without placental study. Purtilo et al. (1977) described numerous placental infarcts, without viral inclusions, in their report of a case of fatal varicella in a pregnant woman and newborn. Balducci and his colleagues (1992) identified in

a prospective study 40 patients with first trimester varicella. Three aborted, one was terminated, and the other 36 patients went to term. One had an omphalocele, and the others were normal. From this information the authors concluded that the risk of the congenital varicella syndrome is small. Enders and her coworkers (1994) did a prospective study of 1373 women with varicella and 366 women who had herpes zoster during the first 36 weeks of gestation. In this cohort, nine cases of congenital varicella syndrome were identified, all occurring when the infection had taken place during the first 20 weeks of gestation. A commentary with additional reports is to be found in the editorial section of the journal (Liesnard et al., 1994). Other reports attest to the uncommon association of fetal disease with varicella pneumonia (Qureshi & Jaques, 1996; Chandra et al., 1998). When fetal disease did occur, as in perhaps three of Qureshi's cases, the placenta showed basal chronic villitis with "occasional multinucleated giant cells." The congenital varicella syndrome of cutaneous scars, limb hypoplasia, chorioretinitis, and cataracts (see Williamson, 1975; Alkalay et al., 1987; Wigglesworth, 1996) was found in only one of 11 infants of women with first-trimester varicella infection studied by Paryani and Arvin (1986). According to these authors, who comprehensively reviewed the topic, infection later in gestation rarely has these fetal sequelae. Magliocco et al. (1992) reported a severely malformed child with numerous destructive lesions that are superbly illustrated. The fetal infection dated from the 12th week of gestation. The placenta showed only old infarcts and calcification. In a 35-week neonate whose placenta we examined, tiny dermal scars, hepatic calcification, chorioretinitis, and CNS involvement were found; the mother had experienced varicella 4 months earlier (Benirschke et al., 1999). At that time, the fetus developed hydrops that subsequently resolved gradually. The placenta had numerous foci of marked VUE with occasional granulomatous appearance. Immunohistochemically and by PCR, varicella (but not HSV) antigen was still present in the many collapsed, occluded villous stem blood vessels. None was found in the inflammatory regions. Many terminal villi had atrophied, primarily those supplied by the occluded stem vessels. This case, and a case of toxoplasmosis, would ordinarily have been diagnosed as VUE, and the point is made in that contribution that new studies need to search more extensively for antigens as possible etiologic agents in the otherwise still disputed nature of VUE. Jones and his colleagues (1994) found only a small risk to the fetus from first trimester varicella infection in their prospective study. Paryani and Arvin (1986) and Brazin et al. (1979) reported that herpes zoster–complicating pregnancy usually has a benign prognosis. The fetus and placenta are typically not affected, although some cases of fetal growth retardation and blindness have occurred. Indeed, Higa et al. (1987), who studied 52 infants of women with varicella during pregnancy, found that 27 suffered anomalies due to the infection when it occurred before 20 weeks' gestation. The placentas were not described. In their review of zoster infections of pregnancy in women who had had varicella in the past, the frequency of anomalies was small. A comprehensive review of varicella infection in pregnancy and the resulting fetal pathology, especially of the nervous system, has been provided by Grose and Itani (1989). Regrettably, they did not address possible placental pathology of this infection. In fact, the placenta of varicella infection in pregnancy has rarely been described. Garcia (1963), who reported two congenital cases, found scattered "firm areas, rice seed–like." He depicted focal necroses. Garcia likened these lesions to granulomas, with epithelioid cells and a giant cell component. Decidual cells contained inclusion bodies. No specific changes were encountered by Saito et al. (1989). They described giant cell pneumonia in a small, prematurely delivered fetus who probably had varicella infection. Immunohistochemical staining of varicella antigens was present on the giant cells in the neonatal lung, but no such antigen was detected in the placenta. It showed merely mild chorioamnionitis. We saw the placenta of a baby with minimal cutaneous scars, chorioretinitis, and seizures. The mother had suffered varicella infection 4 months earlier; then the fetus developed hydrops and cardiac calcifications. They resolved. The placenta had diffuse foci of severe chronic villitis (without plasma cells) and many stem villous vessels were completely obliterated. Immunohistochemistry identified antigen only to the areas of former endothelium in the obliterated vessels. Giant cells were absent, and no inclusions were present.

EPSTEIN-BARR VIRUS

Infection with the Epstein-Barr virus is uncommon during pregnancy. In a few instances, however, congenital infection is believed to have produced congenital anomalies in fetuses. The topic has been reviewed by Ornoy et al. (1982), who studied the induced abortuses of five such pregnancies. They found lesions in all, consisting of deciduitis, villitis with lymphoplasmacellular infiltration, trophoblastic necrosis, and endothelial damage to capillaries. Myocarditis was seen in two fetuses. The cases are circumstantial in that the virus was not shown to be present, but lesions as described are otherwise uncommon at that gestational age. Thus at present one must assume that the virus can affect placenta and fetus. Transplacental transfer of the Epstein-Barr virus to the fetus has rarely been proved. In the few cases where it was shown (Joncas et al., 1981), the placenta was not described. The child described by these authors died from apparently simultaneous CMV infection.

Smallpox, Vaccinia, Alastrim, and Parvovirus B19

Fetal infection with smallpox virus has often been depicted in early obstetrics texts. This virus can readily pass the placenta and cause fetal death and abortion.

Prior to the eradication of smallpox, fetal and placental *vaccinia* occurred occasionally, primarily with primary vaccinations. Wentworth (1966) examined 65 placentas of women who were vaccinated during pregnancy; those mothers did not have an increased abortion rate. Histologic examination and the search for virus inclusions were negative.

Intrauterine infection was well described by Wielenga et al. (1961). The neonate died within a short time and had extensive skin lesions. There were numerous areas of villous and membrane necrosis, and a leukocytic response was present. The lesions were similar to a case we have seen (Fig. 20.60) in which there were extensive necrosis of trophoblast, intervillous fibrin deposits, and focal calcification, but no plasma cells were found. Killpack (1963) also found necrotic foci, "resembling miliary tubercles," and found scanty eosinophilic inclusions. Other descriptions came from Hood and McKinnon (1963) and Naidoo and Hirsch (1963). Garcia (1963) reported macerated stillborns affected with cutaneous *alastrim* (variola minor). Similar granulomatous areas of necrosis were depicted in the placentas accompanying these two fetuses. Guarnieri bodies were present in the decidua.

Infection with *parvovirus B19* is covered in Chapter 16. It is an apparently frequent cause of fetal anemia because of the preferential infection of erythrocyte precursors by this virus. Hartwick et al. (1989) have shown parvovirus B19 in a dot-blot hybridization study of a 9 weeks' gestation fetus. Considerable vascular endothelial damage was present in the embryo and placenta. In a portion of one umbilical artery the endothelium and muscle were partially destroyed, and in main stem vessels perivascular lymphocytic infiltration was seen. The lymphocytic infiltration was composed of cells belonging to the cytotoxic or suppressor T-cell variety. There is a provocative discussion of the origin of these inflammatory cells that bears relevance to the topic of "villitis of unknown origin" (vide infra). Despite the fact that, heretofore, the embryo was not believed to be capable of mounting an immunologic response at this stage of development, the authors gave cogent reasons for assuming that the T cells they identified were not of maternal origin. Interestingly, inclusions were absent in the red blood cell precursors of this embryo but were found in skeletal muscle cells. In an important study of presumed parvovirus B19 infection of the fetus, de Krijger et al. (1998) showed that the presence of putative inclusion bodies is not diagnostic of this infection. They uncovered many such inclusions as artifacts, and asserted that confirmation by PCR is mandatory. There is now excellent evidence that clinical outcome is correlated with the degree of trophoblastic apoptosis (Jordan & Butchko, 2002). These authors showed that the B19 receptor (globoside-containing) is present not only on red cells precursors but also on trophoblast, and that gestations with poor fetal outcome had a much greater degree of trophoblastic apoptosis than those with better results. The difficulty of making the correct diagnosis, especially in nonhydropic fetuses, is highlighted in a paper by Tolfvenstam et al. (2001). Only three of nine DNA-positive cases had erythroid inclusions; this led them to suggest that many more unresolved stillborn infants would have a diagnosis assigned if DNA study were added to the autopsy protocol. An additional problem in the diagnosis of parvovirus B19 diagnosis is the development, temporally different, of two distinct antibodies—linear and conformational (Jordan, 2002).

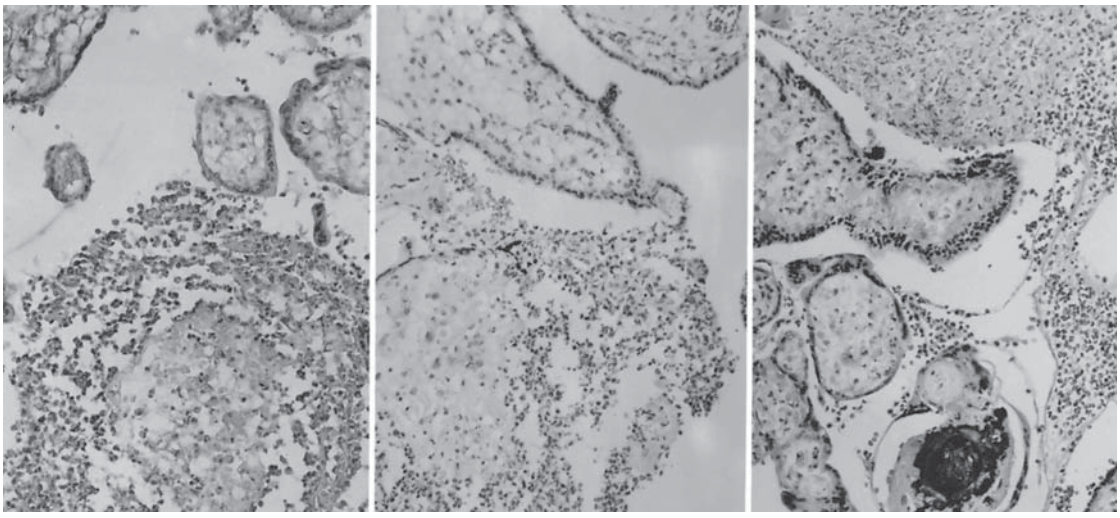

FIGURE 20.60. Vaccinia during pregnancy. Many villi are necrotic, and an intense inflammatory reaction is seen around their remnants. Note the focal calcification of the necrotic area at bottom right. H&E ×160. (Courtesy of Dr. B. Ivemark, Stockholm, Sweden.)

Samra et al. (1989) reviewed all reports on parvovirus infection of the fetus and concluded that the virus passes the placenta readily. They described a stillborn, hydropic fetus in whose placenta there were villous necrosis and calcifications. Infection with different species of parvoviruses has been shown to cause a wide spectrum of diseases in different animals, including congenital anomalies. The subject has been reviewed in detail by Margolis and Kilham (1975), who make reference to human conditions.

ENTEROVIRUSES

Transplacental *poliomyelitis* infection has been described, and the virus was isolated from the placenta in some of these cases (Barsky & Beale, 1957). No pathologic lesions of the placenta are known.

Infection with **enterocytopathogenic human orphan (ECHO)** and **Coxsackie** viruses occurs commonly during the neonatal period and may have serious consequences in neonates. When infection occurs during pregnancy, the fetus is usually spared, perhaps protected by maternal antibody transfer (Amstey et al., 1988). Amstey et al. also perfused two placentas with a mixture of viruses and found them not to transfer. Nevertheless, transplacental passage and fetal infection have occasionally been shown for ECHO viruses (Hughes et al., 1972; Modlin, 1986; C. Davis, personal communication, 1985), and for Coxsackie B virus (Kibrick & Benirschke, 1958; Sauerbrei et al., 2000). There is also speculation that such prenatal infection may be a cause of juvenile diabetes. The placentas of the few cases proved to have caused prenatal Coxsackie virus infection have shown occasional meconium staining, but other meaningful changes were usually absent. Fetal hydrops secondary to myocarditis has occurred with Coxsackie virus infection; placental lesions were not apparent in that abortus (Benirschke et al., 1986). Garcia et al. (1990) described three perinatal deaths from ECHO 33 and 27 infections with isolation of virus from placentas and fetal tissues. They described villitis and intervillositis in the placentas that may best be likened to VUE (vide infra). The same authors expanded on these findings in 1991. Interestingly, the viruses did not affect the fetus, while they were isolated from the placentas, many of which had typical chronic villitis. Some also suffered mural thromboses and vascular lesions in the umbilical cord. The electron microscopy is not convincing, but is also not expected to contribute in these RNA virus infections.

Batcup et al. (1985) reported villous necrosis and severe intervillositis in the placenta of a patient who had Coxsackie virus A9 meningitis at 33 weeks' gestation. A stillborn, macerated fetus was delivered 5 days later, and the virus was recovered from the placenta. Moreover, there were mild myocarditis and early meningitis in the fetus. Remarkably, the placenta had massive intervillous fibrin deposits, much as one sees in the *gitterinfarkts*, discussed in Chapter 9. Villous stem vessels had mural thrombi, and many aspects of the placenta showed features that are usually designated as VUE (vide infra). It is difficult to believe that the extensive placental alterations depicted in their report, could have arisen within this short time span, but further observations to investigate this possibility are clearly mandated.

Ogilvie and Tearne (1980) described three abortions during episodes of infection with Coxsackie A16 virus (hand, foot, and mouth disease) and recovered the virus from one placenta. The pathologic features of the placenta, however, were not discussed.

INFLUENZA, MUMPS, RABIES

Transplacental **influenza A2** (Hong Kong) infection was reported by Yawn et al. (1971). The virus was recovered from the fetus and amnionic fluid in the fatally ill gravida. Fetal tissues and placenta were found to be structurally normal. In an abortus delivered during the febrile period of parainfluenza-1 virus infection, Lavergne et al. (1969) observed a normal placenta. McGregor et al. (1984) recovered influenza A/Bangkok virus from maternal secretions and amnionic fluid of an acutely ill patient who appeared to have the amnionic fluid infection syndrome. The pregnancy continued, and a normal birth ensued. The placenta was not described, but transplacental infection was inferred. Conover and Roessmann (1990) reported the autopsy findings of a malformed infant in whose brain influenza virus was identified immunohistochemically. The placenta was not described.

Fetal **mumps** virus infection may occur, and it has been suggested that some congenital anomalies are due to this agent. Virus has been recovered from the placenta, but no histopathologic change has been described (Yamauchi et al., 1974). Herbst et al. (1970) found only ultrastructural changes in the placenta of a patient with mumps. Severe villous necrosis, simulating that of herpes simplex virus, was found in three cases of intrauterine mumps infection described by Garcia et al. (1980). They also reviewed the sparse and contradictory literature. Small cytoplasmic inclusion bodies were depicted in the decidua.

Transplacental **rabies** infection is not known to occur in women. Spence et al. (1975) observed two normal fetuses after maternal rabies complicated pregnancy. The placenta was not described.

Hepatitis

Transplacental infection with hepatitis viruses has been reported; the topic was reviewed by Altshuler and Russell (1975) and Snydman (1985). Because hepatitis A viremia is short and a carrier state does not occur, fetal infection with this virus is rare but is well documented. Leikin et al. (1996) described fetal ascites and subsequent meconium peritonitis in a fetus whose mother became infected at 20 weeks' gestation. The placenta was not described; other cases of fetal ascites are on record, and McDuffie and Bader (1999) attributed meconium peritonitis to transplacental infection. Asymptomatic hepatitis B infection, however, was found to occur in 0.66% of a low-risk population (Christian & Duff, 1989). Two studies have shown that the antigen passes the placenta (Wang & Zhu, 2000; Xu et al., 2001), and the latter publication traces the virus by fluorescence microscopy. Transmission of hepatitis C virus from chronically infected mothers to fetuses occurs but appears to be uncommon (Thaler et al., 1991; Wejstal et al., 1992; Silverman et al., 1993; Hunt et al., 1997). Gibb et al. (2000), in their review of 441 mother–child pairs, estimated the transmission rate as 6.7% and suggested that it was enhanced in HIV infection. Placentas from such cases of vertical transmission have not been described in the literature, but the ones we have seen have been entirely normal. Vertical transmission of the newly delineated hepatitis G virus has also been reported (Feucht et al., 1996; Inaba, 1997) without placental study. Lin et al. (1996) proposed that transplacental blood contamination may occur during labor.

In contrast to hepatitis A, the high carrier state of hepatitis B virus in adults is a potential hazard to many fetuses. It is generally agreed, however, that this virus is usually acquired enterically during birth or thereafter;

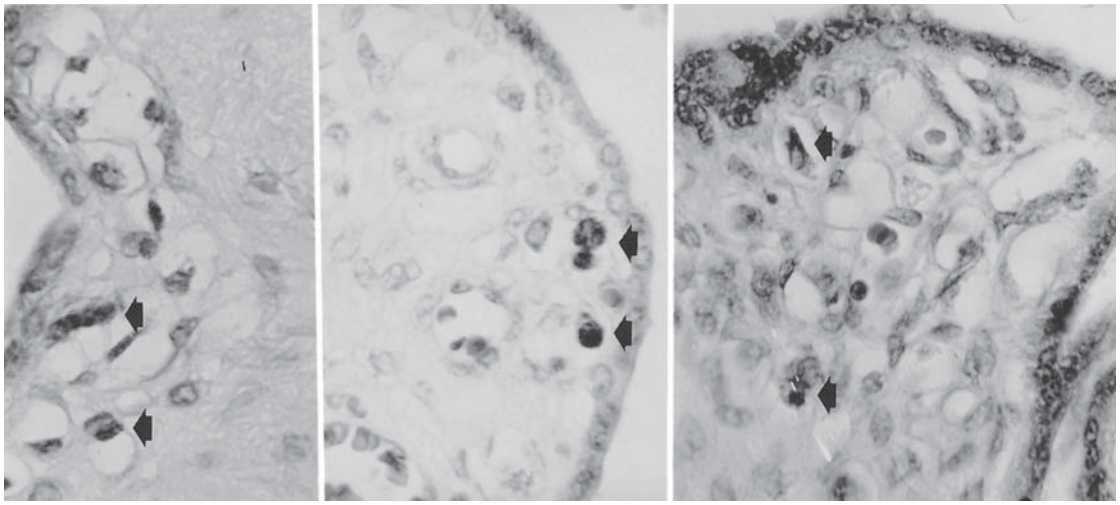

FIGURE 20.61. Placenta with hepatitis B. Pregnancy was interrupted at 20 weeks' gestation. Hofbauer cells are filled with bilirubin (arrows), but there was no inflammation. H&E ×240 (left, center); ×640 (right), red filter.

nevertheless, the transplacental acquisition of hepatitis B virus has occasionally been verified (Fawaz et al., 1975; Mulligan & Stiehm, 1994). Mitsuda et al. (1989) found positive cord blood once in 10 patients but showed that the antigen was present in colostrum of eight patients using the sensitive PCR method. Prospective studies of aborted fetuses from virus-carrying mothers showed that four of 48 fetuses (8%) were thus infected (Li et al., 1986).

The placenta has rarely been examined by pathologists. Altshuler and Russell (1975) stated that the placenta shows "relative immaturity." Buchholz et al. (1974) described the placenta of an infected infant delivered by cesarean section as showing "placental insufficiency." Studies with direct and indirect immunofluorescence indicated the presence of antigen, confined to the basement membranes of the (infantile part) of cells. The authors were uncertain that the placental insufficiency was caused by the infection.

Lucifora et al. (1988) studied the placentas of three asymptomatic hepatitis B surface antigen (HBsAg) carriers with immunohistochemistry. All showed strong reactivity of the Hofbauer cells and villous endothelium, but no pathologic changes were noted. Lucifora et al. (1990) then detected the hepatitis B core antigen (HBcAg) histochemically in all placentas of symptom-free carriers. It was again primarily localized in trophoblast and Hofbauer cells, but also found in fetal endothelium and fibroblasts. They suggested minor pathologic changes (edema, congestion) but are not convincing. We described the placentas of two patients with active hepatitis (Khudr & Benirschke, 1972). The only abnormal finding was the presence of large amounts of bilirubin in Hofbauer cells and chorionic membrane macrophages. There was neither degeneration nor inflammation. The pigment bleached readily when slides were exposed to light, apparently similar to that of meconium macrophages. We have seen the placenta and fetus of a patient who had a therapeutic abortion for hepatitis B. The patient was still icteric when the procedure was done. The fetus, umbilical cord, and membranes were entirely unstained and normal; however, the villous tissues were the color of marmalade, a deep yellow-green. Histologically, numerous deeply bilirubin-stained macrophages were present as villous Hofbauer cells (Fig. 20.61). Some syncytial trophoblastic cells and the membranes had relatively few stained cells. Focal syncytial cell necrosis was present, but there was no inflammation or obvious villous necrosis. There was intense enteritis of the fetus, with meconium deposits and eosinophilic leukocyte infiltration in the submucosa. Several intestinal ulcers were present, and in some areas the bowel was nearly perforated. We assumed that the fetus may have become infected by swallowing amnionic fluid. The case further indicates that bilirubin may traverse the placental barrier but that it then becomes trapped by villous Hofbauer cells.

Rubella (German Measles) and Other Viral Infections

The fetal rubella syndrome exemplifies transplacental fetal virus infection, but because of vaccination, rubella is now uncommon. Banatvala and Brown (2004) report an updated survey of the global infection rate and summarize the most recent diagnostic tools available. A variety of characteristic anomalies are produced in the fetus when infection occurs early, and the precise mechanism by which the degenerative changes responsible for the fetal rubella syndrome, such as cataracts, are generated has been a matter of intense investigation in the past.

Many investigators have detected the virus in the placenta, amnionic fluid, and abortus by virologic means (Alford et al., 1964; Thompson & Tobin, 1970; Catalano et al., 1971). When they isolated the virus from products of conception, Monif et al. (1965) suggested that many macerated fetuses died from placental, rather than fetal, infection. Töndury (1951, 1952a,b, 1964), in numerous contributions, has championed the idea that the fetal damage resulted from embolism of virus-damaged fetal (placental) endothelial cells. Others have suggested that the damage is due to chromosomal breakage.

Endothelial damage in villi of infected products of conception was confirmed in the large study conducted by Driscoll (1969) and by the finding of "endangitis obliterans" in about 40% of the stem villous vessels of infected cases seen by Horn and Becker (1992) and Horn et al. (1993). Driscoll further described sclerosing villous inflammation, which she interpreted to possibly be responsible for the growth retardation. Töndury and Smith (1966) observed focal trophoblastic necrosis and elaborated on their idea of extensive damage to the villous capillary endothelium in early embryos with rubella infection (Fig. 20.62). Selzer (1963, 1964) described basophilic inclusion bodies, but they have not been reported in other descriptions of placental lesions. Similar lesions have been described in a report of 45 cases interrupted because of gestational rubella infection (Ornoy et al., 1973). They discovered some placental lesions in all cases that resulted in malformed fetuses. Decidual perivascular round cell infiltration was prominent; in villi of early gestations, necrosis and fibrosis were found, and swollen Hofbauer cells were prominent. Vascular inflammation was also a prominent finding, similar to that reported earlier. These authors described inclusions in trophoblast and villous stroma but did not depict them, and other authors (Horn and Becker, 1992; Horn et al., 1993) were unable to identify inclusion bodies. It must be pointed out also that the endothelial abnormalities described are neither diagnostic nor present in all cases of virologically confirmed cases of rubella. Moreover, some of these changes are also observed in stillbirths unrelated to virus infections; thus, a degree of skepticism is needed in their interpretation.

The attenuated strain of rubella vaccine virus has been isolated from placentas and fetuses, but villous lesions have not been observed (Phillips et al., 1970; Vaheri et al., 1972). Only Larson et al. (1971) described "histologic changes in placenta or decidua consistent with rubella infection." The fetuses were normal, and apparently only decidual changes were detected.

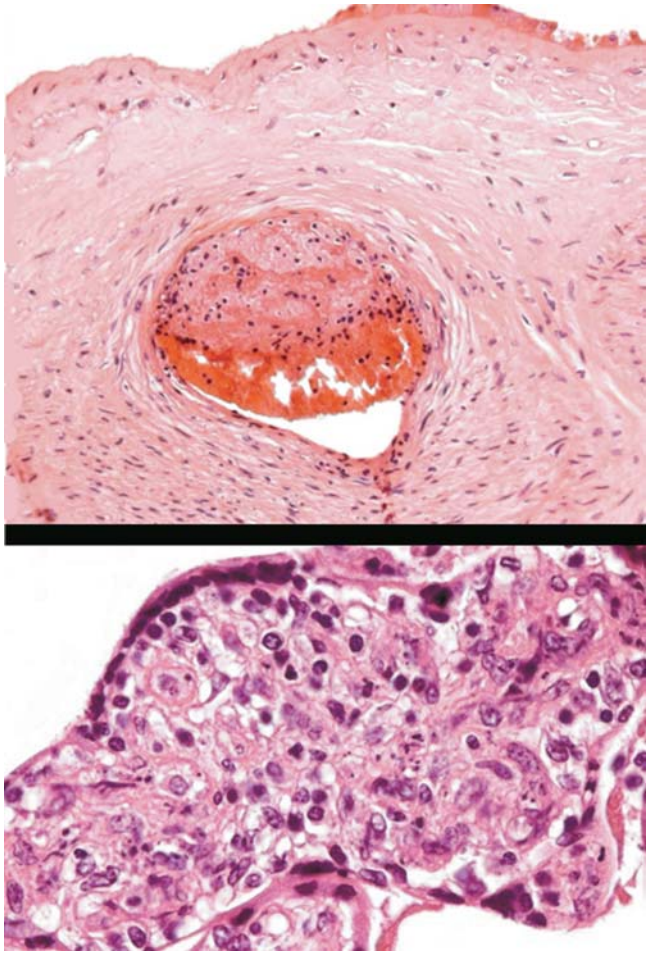

FIGURE 20.62. Sections of immature placenta from rubella-infected fetus. Note the mural thrombosis and nucleated red blood cells (NRBCs) in surface vessel (top) and round cell infiltration of villi (bottom).

Rubeola (Measles)

Measles in pregnancy has been very uncommon and its consequences have been described only rarely. There is, however, an extensive database from the 1951 Greenland and the United States epidemics as to the effects of measles on pregnancy. The infection is apparently not teratogenic, and a significantly increased fetal mortality may relate primarily to fever. Access to this literature is provided by Stein and Greenspoon (1991). Placental disease has now been described, but congenital measles apparently does not exist (Eberhart-Phillips et al., 1993). The only report with identification of the antigen in the placenta is the case of Moroi et al. (1991). Their patient suffered fetal demise at 25 weeks after an acute infection, and the virus was detected in the decidua and syncytiotrophoblast by immunohistochemistry. It was not found in the fetus. The placenta was firm and infiltrated with an excessive amount of fibrin and mononuclear cells. Stein and Greenspoon (1991) described three cases: one had an unexplained intrauterine fetal demise (true knot of cord, 30% placental infarct), and the other two did well. Placental lesions were not described, and fetal infection

was not apparent. However, Ohyama et al. (2001) described in detail the placenta and clinical findings of a monochorionic set of twins in which one was a macerated stillborn and the other survived without evidence of measles. The placenta of the stillborn had extensive fibrin deposits, and measles virus was definitively shown to be present in trophoblast (by electron microscopy and immunologically). The mother had become infected at 19 weeks and one twin died at 32 weeks. There were large surface inter-twin anastomoses present. It remains uncertain whether the fetus died from measles infection or because of MZ-twin vascular problems; nevertheless, the presence of inclusion bodies and their demonstration as virus in trophoblast is not doubted.

Human Immunodeficiency Virus Infection

Infection of the fetus with the human immunodeficiency virus (HIV) has frequently been reported (Berrebi et al., 1987; European Collaborative 1988; Sperling et al., 1989), but the exact time and mode of this vertical transmission is disputed. Moreover, perhaps because this transmission occurs often at the time of delivery, the treatment of HIV-positive mothers with azidothymidine (AZT) has led to a marked reduction of neonatal HIV infection. Pascual et al. (2000) found no virus transmission in early gestation; but other reports have differed. Therefore, the detailed review by Miller et al. (2000) is most helpful. It weighs the pros and cons of studies of this controversial topic; it discusses whether the immunologic stains of placental tissue are powerful enough to demonstrate the virus and, importantly, whether coexisting chorioamnionitis enhances virus transfer. But one result is universal: HIV infection of the placenta (if it occurs at all) leaves no specific lesions that can be diagnosed without equivocation. Indeed, experimental infection of trophoblast or placental lobules in vitro is usually impossible. The prevalence of HIV infection was studied in an obstetrical population by Barton et al. (1989). They found antibodies only in patients with risk factors (7.1%), whereas those without risk factors were negative. AIDS has occurred in some of the offspring, and the vertical transmission rate of HIV is estimated to be 24% (European Collaborative Study, 1988). Nevertheless, Katz and Wilfert (1989) were uncertain that the infection occurred transplacentally rather than during delivery. Their editorial discussed at length the reports of neonatal AIDS presented in the same journal issue. Fetal deaths and prematurity have been seen in women infected with HIV, but many of these patients had other problems that may have been responsible (Gloeb et al., 1988). Nevertheless, maternal HIV-1 infection is associated with prematurity and endometritis, whereas fetal growth retardation was not observed in the study conducted by Temmerman et al. (1994). These authors were also unable to identify histopathologic abnormalities in the placentas. Monozygotic twins discordant for HIV infection and with a single placenta were reported by Menez-Bautista et al. (1986). The MZ twins had presumably been exposed to the agent only during fetal life. Alger et al. (1993) found no adverse effect upon pregnancy performance in women who are infected with HIV and showed that an HIV embryopathy does not exist.

The virus has been isolated from amnionic fluid (Mundy et al., 1987) and perhaps from the placenta (Hill et al., 1987). In the latter report, HIV was obtained from placenta but not from lochia, the infant, and cord blood. The infant was well; an electron micrograph of an infected T cell accompanied the report, presumably infected with virus from this placenta's culture, but the authors suggested that the isolation may reflect maternal blood infection. The report was criticized by Peuchmaur et al. (1989), who, subsequent to this report, failed to isolate HIV from placental samples. Greenspoon and Settlage (1989) also believed that the virus of this placenta was more likely contained within the maternal blood of the placenta; the child has remained well, now age 3 years. Since those reports, Soeiro et al. (1992) identified HIV-1 in 30% of fetal material from first trimester abortuses by PCR of HIV nucleic acid. Yet only one of eight infected abortuses showed positive in situ hybridization signals.

Brady et al. (1989) used immunoperoxidase stains on placentas of HIV-infected patients. They found positive staining, particularly in Hofbauer cells, and suggested that this presence of viral protein in placental macrophages might present a reservoir for perinatal infection. A morphologic study of the placentas of 49 HIV-infected patients was undertaken by Jauniaux et al. (1988). The light-microscopic findings were unremarkable. No significant alterations were seen, and the lesions were nonspecific. An ultrastructural study showed "retrovirus-like particles" in the syncytiotrophoblast of one induced abortus's placenta. Five other mature placentas showed isolated virus particles. They were similar to the C-type particles described formerly in many human placentas. Lewis et al. (1990) have demonstrated the presence of HIV by immunocytochemistry and in situ hybridization in maternal decidual leukocytes, trophoblast, Hofbauer cells, and embryonic blood cell precursors of aborted specimens (Fig. 20.63). Although the specific CD4 receptors were not identified on the trophoblastic surface, the authors referred to experiments with trophoblast culture that have demonstrated CD4 presence. It was suggested that transmission (around 30%) occurs directly, without transfer of maternal leukocytes being a prerequisite, as had been postulated. On the other hand, in a sizable prospective study of 44 patients with viremia, Ehrnst et al. (1991) found no transplacental HIV transmission to the 27 infants born. In only one of seven placentas was the virus identified. Andiman et al. (1990) similarly had a

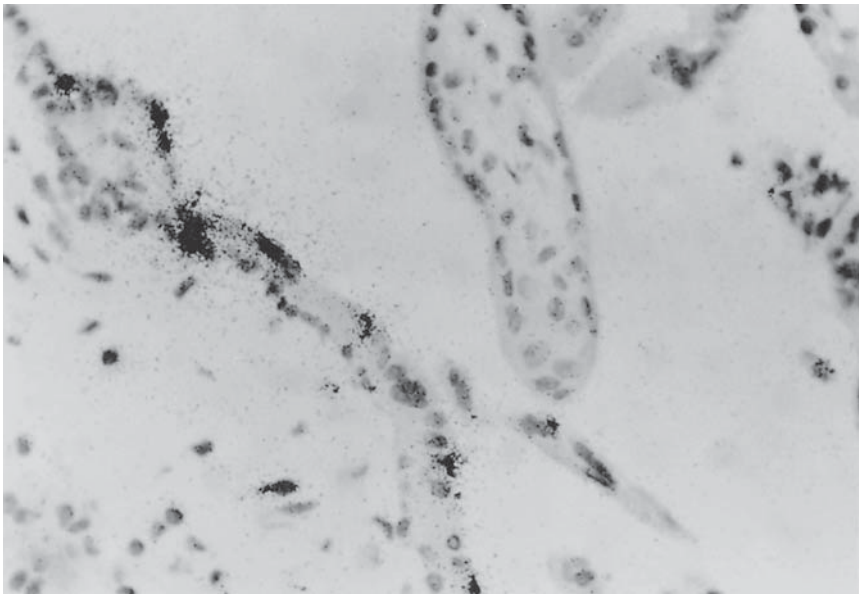

FIGURE 20.63. Eight weeks' gestation villi of HIV-1 infected mother. Specimen was hybridized with ^{35}S-labeled probe. Syncytium, Langhans' cells, and Hofbauer cells are labeled. Hematoxylin ×312. (Courtesy of Dr. S.H. Lewis, formerly of New York, New York.)

low vertical transmission rate but also did not examine the placentas. That placental explants can support growth of HIV was shown by Amirhessami-Aghili and Spector (1991). They cultured first-trimester villous tissue, infected it, and demonstrated the presence of the CD4 and HIV antigens; surprisingly, hCG and progesterone production rose in infected cultures. When Katz et al. (1997) sought markers for formalin-fixed placental localization of HIV, the nucleic acid was seen in syncytiotrophoblast by ^{35}S RNA in situ hybridization. The histopathologic findings, however, were unimpressive, with minor (nonspecific?) inflammatory reactions that are not truly diagnostic of infection. We have also not been able to detect histopathologic placental changes in patients with the infection. It has also been pointed out that unusual tumors metastatic to the placenta may signal HIV infection. Pollack et al. (1993) described a patient who had abdominal delivery for fetal distress. The grossly normal placenta (it had white granular areas on the maternal surface) had intervillous infiltrates by "sheets of small noncohesive, round tumor cells." This was diagnosed as non-Hodgkin's lymphoma. The mother developed further signs of AIDS, but the infant remained normal.

Kalter et al. (1973) had found **C-type particles** in four of six normal human placentas at the junction of syncytiotrophoblast and basement membrane. Their "budding" was more common in premature placentas. Other investigators have shown cross-reactivity of these particles to certain retroviruses (Sawyer et al., 1978; Maeda et al., 1983), and similar structures have been detected in many nonhuman primate placentas (Panem, 1979). C-type particles are nearly ubiquitous viruses, parasites, whose functions are presently unknown. Imamura et al. (1976) detected these RNA-virus–like structures in the placenta of a patient with lupus but also in normal placentas, albeit in smaller numbers. They also described "tubuloreticular inclusions" in villous endothelium from patients with lupus erythematosus. Similar structures have been induced in Hofbauer cells by maternal interferon therapy in rhesus monkeys (Feldman et al., 1986).

The significance of all of these findings with respect to true viral infections remains uncertain, but congenital HIV infection occurs with certainty (see Goedert et al., 1989). Indeed, the neonatal mortality is significant, and most cases manifest during the first year of life (Scott et al., 1989).

Dengue virus transmission to the fetus has been described only a few times, but placental lesions are unknown. Boussemart et al. (2001) described two such neonates and summarized earlier reports. **West Nile Virus** transmission to the fetus has once been described (Alpert et al., 2003). The neonate had chorioretinal damage and CNS abnormalities, but the placenta was not described.

Toxoplasmosis

Toxoplasmosis is caused by the coccidian *Toxoplasma gondii*, a pan-global parasite of cats and other felids. In cats, a well-explored life cycle exists in the intestinal epithelium. Oocysts are shed in the stools of infected animals. Rodents and other animals ingest these oocysts and acquire the disease. Cats, preying on infected rodents, complete the cycle. The disease is also widespread in domestic animals.

There are several excellent reviews on congenital toxoplasmosis (Kirchhoff & Kräubig, 1966; Frenkel, 1973, 1974; Dubey, 1977; Dubey & Beattie, 1988; Sever et al.,

1988; Freij & Sever, 1996; Montoya & Liesenfeld, 2004). Frenkel (1971) presented a particularly good consideration of all aspects of this disease. The human infection is acquired in adults by two means: (1) contamination with oocysts from feces of infected cats; and (2) ingestion of cysts and tachyzoites in raw, infected meat—largely pork and mutton (Kean et al., 1969). Pregnant women should not eat undercooked or raw meat, and they should also avoid having contact with "wild" (i.e., hunting) cats. Heating to 150°F kills the organism. Cats raised solely on commercial diets are not infected; cats that hunt and are given raw meat may become infected. Emptying their litter box daily to prevent drying and dust-producing feces is recommended (Kimball et al., 1974). A thoughtful review of these aspects has been written by Swartzberg and Remington (1975). Of the Parisian human adult population, 84% have antibodies because of the frequency of raw meat consumption in France.

Transplacental toxoplasmosis is not uncommon. It has been well described to cause severe destructive disease in the offspring who are infected during early gestation. Minor degrees of damage are incurred when infection develops later in pregnancy. Chorioretinitis, encephalitis with hydrocephaly, and other organ involvement may nevertheless cause crippling disease. Wilson and Remington (1980) estimated that the lifetime support for the 3300 children born annually in the United States with toxoplasmosis is the staggering sum of over $200 million.

It is generally assumed that almost all, if not all, congenital *Toxoplasma* infections occur when a woman has her primary infection during pregnancy. Few reports exist that congenital toxoplasmosis occurs in successive pregnancies. It has also been assumed that the presence of maternal antibodies prevents fetal infection. That this is not so was shown by the important case detailed by Forther et al. (1991). They found a toxoplasma cyst in an abortion specimen from an immune patient who had contact with an infected cat that caused acute toxoplasmosis in her brother. Feldman (1963) has doubted that recurrent infection ever occurs. Desmonts and Couvreur (1974) have provided the most conclusive prospective study of toxoplasmosis in pregnancy. Almost 45% of Parisian women with primary infection during pregnancy had infants with congenital toxoplasmosis. The rate of infection increased with the gestational trimesters (17%, 25%, and 65%, respectively). Fetal destruction was the most severe during early, rather than late, gestation. The authors were skeptical that toxoplasmosis causes abortion and denied the occurrence of repeated congenital toxoplasmosis. Others have found *Toxoplasma* organisms in the placenta and uterus of infected, macerated fetuses (Mellgren et al., 1952) or have isolated it from spontaneously aborted products of conception (Remington et al., 1964; Forth et al., 1991). Stray-Pedersen and Lorentzen-Styr (1977) studied endometrial biopsies of women with habitual abortion. Six of 96 women had tachyzoites in endometrium and menstrual blood, demonstrated by fluorescent antibody studies, but none was isolated in mouse inoculations. Treatment of these women abolished the organisms.

Because it is often difficult to positively identify the organism in routinely stained placental material, the method by which the organism is verified in tissues is of great importance. It is easiest to demonstrate toxoplasma by placing ground tissue samples into the peritoneal cavity of young mice or into appropriate tissue culture cell lines (Kaufman & Maloney, 1962). Handling this organism, however, is often avoided because of the hazards of infection. Immunologic means are generally preferred, although the results are often dubious. For positive identification in tissues, Dallenbach and Piekarski (1960) have advocated the fluorescence antibody technique. A similar methodology was used by Foulon et al. (1990a) in identifying the antigen from tissue cultures infected with chorionic villus sampling (CVS) specimens. The electron microscopic appearance of *Toxoplasma* cysts ("pseudocysts") is characteristic and has been well shown by Callaway et al. (1968). Detailed considerations of modern diagnostic tests for toxoplasmosis have been given in a review of all aspects of this disease by Koskiniemi et al. (1989). Savva and Hollman (1990) reviewed the PCR methodology that allows unequivocal detection of the toxoplasma DNA (see also Hohlfeld et al., 1994; Fricker-Hidalgo et al., 1998). The problems of prenatal diagnosis were considered by Foulon et al. (1990b), who had much success with amnionic fluid culture and funipuncture.

The organism has been isolated from amnionic fluid and placentas of infected pregnancies (Stray-Pedersen, 1980; Teutsch et al., 1980). The diagnosis of congenital infection was later made by fetal blood sampling, which led to beneficial prenatal therapy in some cases (Desmonts et al., 1985; Daffos et al., 1988). Foulon et al. (1999) found that fetal infection was best made with amnionic fluid PCR and culture, rather than by cordocentesis. Couvreur et al. (1976) described congenital toxoplasmosis in 14 twins. In two of these pairs, only one twin was affected. Although it is stated that these twins were dizygotic, one of the two had a DiMo placenta, and they thus must have been identical twins. The authors reviewed previous reports of discordant dizygotic (DZ) twins, whereas all MZ twins had been similarly affected. Cox et al. (1987) also reported two discordant twins when they assayed fetal blood during pregnancy for antibodies.

Evidence of congenital disease is at times difficult to find. It may require a long follow-up. Thus, the MZ twins reported by Glasser and Delta (1965) were judged to be normal at birth. Their placenta had many cysts in the membranes but no other pathologic features. The chil-

dren first became symptomatic at 7 months of age. Another set of twins, described by Miller et al. (1971), also had late onset, and toxoplasmosis was not suspected until hydrocephaly developed. The mother had eaten ground beef during the pregnancy, the presumed source of infection. Late onset of symptomatology was further explored by Koppe et al. (1986), who showed that in children with congenital toxoplasmosis "new lesions continue to appear well after the age of 5 years, and the impairment can be severe." In other cases of apparent fetal well-being despite maternal infection during pregnancy, the maternal therapy may have prevented fetal disease (e.g., Hammer & Wegmann, 1966).

Placental infection with *Toxoplasma* has been well documented. It is presumably always produced by organisms circulating in the maternal blood, although the isolation of cysts from endometrium in chronic aborters makes direct infection from the endometrium possible (Werner et al., 1963). Altshuler (1973b), who described a fatal case with placental study, bemoaned that the placenta is not studied more often in this disease and suggested rapid means for identification of the organism. The case he studied was typical. The infant had hydranencephaly, a frequent feature of this disease (Larsen, 1977), hepatosplenomegaly, and hydrops. Hydrops in congenital toxoplasmosis has been described repeatedly. Typical cysts were present in the subamnionic/chorionic tissues, and they were unaccompanied by inflammation. It is only when the cysts rupture that a local plasmacellular reaction and necrosis take place. Altshuler found a marked increase in villous Hofbauer cells, erythroblasts in the fetal circulation, and vascular proliferation in placental villi. He also depicted a lymphocytic-plasmacellular villitis (Fig. 20.64).

Similar villitis, including necrosis and villous *Toxoplasma* cysts, were found by Elliott (1970) in the placenta of a 3-month macerated abortus. He described the placenta as being "shaggy." Becket and Flynn (1953) found the placenta in toxoplasmosis to be as pale as it is in cases of erythroblastosis. They depicted the cysts in villi in both of their cases. Driscoll noted that in most of her cases marked plasmacellular deciduitis was a pronounced feature (Benirschke & Driscoll, 1967). Excellent illustrations of cysts within villi, occurring apparently even within trophoblast, were provided by Werner et al. (1963). They considered it to be the result of transmission from infected endometrium. Edwina Popek (1992) described granulomatous villitis in an 18-week stillbirth with intensive chronic villitis; she also reviewed the literature on placental toxoplasma infection in this contribution. Popek found organisms in every section of her case and was able to stain them immunologically. Nevertheless, careful study identified the organisms without additional aid. There were no plasma cells in the villi.

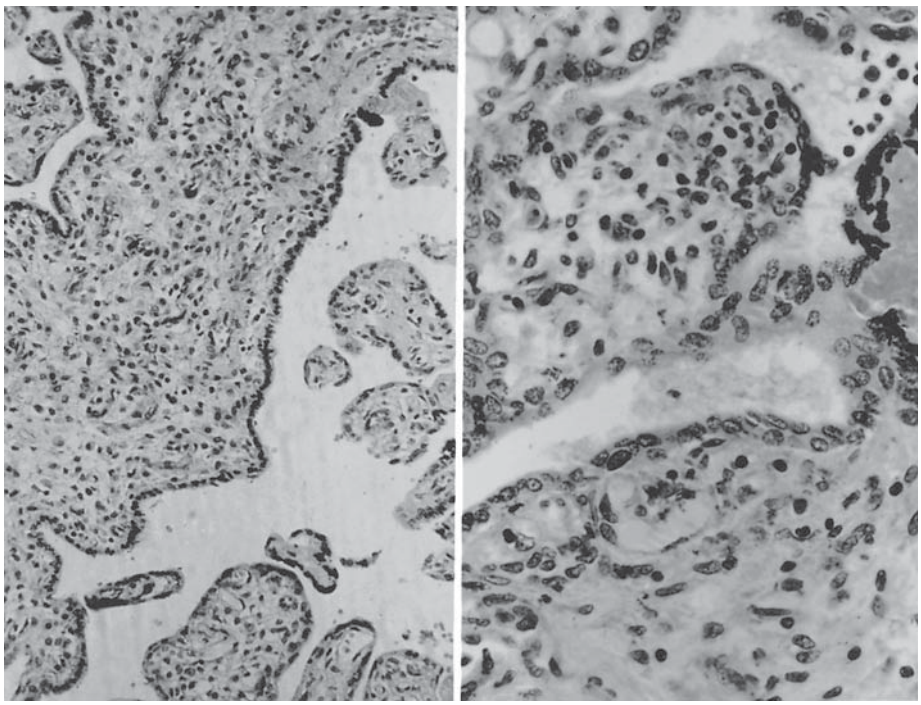

FIGURE 20.64. Villi in a patient with congenital toxoplasmosis. Left: Same case as in Figure 20.66. Right: Same case as in Figure 20.65. There is a diffuse lymphoplasmacytic infiltration, with sclerosis of the villi. H&E ×125 (left); ×240 (right). (Courtesy of Dr. G. Khodr, San Antonio, Texas, and Dr. J. Hustin, Loverval, Belgium.)

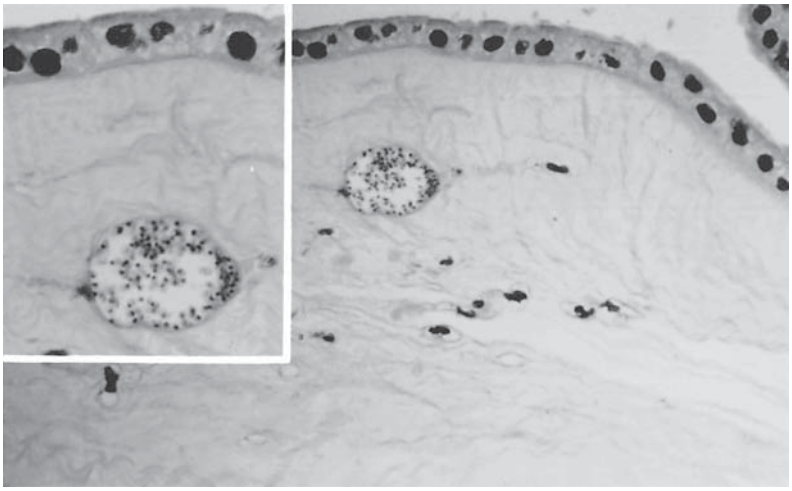

FIGURE 20.65. *Toxoplasma* cysts in amnion/chorion of a child with congenital infection and hydrocephaly at 31 weeks' gestation. Inset: Enlargement of a cyst. H&E ×640. Inset: H&E ×1200 (Case courtesy of Dr. Jean Hustin, Loverval, Belgium.)

Although the cysts depicted by these authors are classical, care must be taken with the interpretation of *Toxoplasma* cysts in other publications. In consultation, we have seen several cases where cysts had been suspected; they were, however, degenerating syncytium. The photographs shown by Sarto et al. (1982) of syncytial nuclei in "endomitosis" simulate *Toxoplasma* cysts. They must not be mistaken for the organism. Janssen et al. (1970) have discussed these difficulties and urged that these problems must be borne in mind when toxoplasmosis is diagnosed from slides. As difficult as cyst identification is, the diagnosis of tachyzoites in histologic sections is impossible. Without fluorescent antibody staining or smears of infected tissue, they usually cannot be recognized with certainty. Dr. Jean Hustin (Belgium) has made available to us a case of a primary infection at 24 weeks' gestation that was treated with spiramycin. Despite this therapy, the fetus developed hydrocephaly and was aborted at 31 weeks. Numerous cysts were found in the chorion (Fig. 20.65), and plasmacellular infiltration, with necrosis and fibrosis, was found in villi. This maternal therapy is thus ineffective in combating the infection.

In toxoplasmosis, as in CMV infection, thrombosis of chorionic vessels occurs (see Fig. 20.67). The thrombi and vessel walls may be calcified, even vessels of the umbilical cord have been thus calcified (Khodr & Matossian, 1978). Pathologists are frequently challenged to provide a specific diagnosis when chronic villitis is found. They must then find cysts, proceed with antibody staining (Fig. 20.66), or, best, isolate the organism by injecting tissue homogenate into the peritoneal cavity of mice. Tissue culture methods of identification may also be used. Occasionally one may find cysts only in the umbilical cord, perhaps because they stand out better (Benirschke et al., 1999). But when calcified vessels of the placenta remain unexplained, especially when some chronic inflammation of villi is also encountered, a detailed search for toxoplasma cysts needs to be undertaken.

The questions of whether recurrent toxoplasmosis occurs and with what frequency are not resolved. Kimball et al. (1971) conducted a prospective study of 5000 obstetrical patients and came to the conclusion that abortion is significantly associated with antibodies to *Toxoplasma*, but in none of their 260 abortion specimens could they show the organism. Moreover, habitual abortion was not due to toxoplasmosis in the mother. Feldman (1963) thought that recurrent toxoplasmosis does not occur. Others are dubious or believe that recurrent infection is most likely associated with immunosuppression. Langer (1963a,b) first suggested that toxoplasmosis may be a cause of spontaneous abortion. He inoculated mice with material from 70 repeat aborters and isolated organisms from 23 of them. However, he also obtained organisms

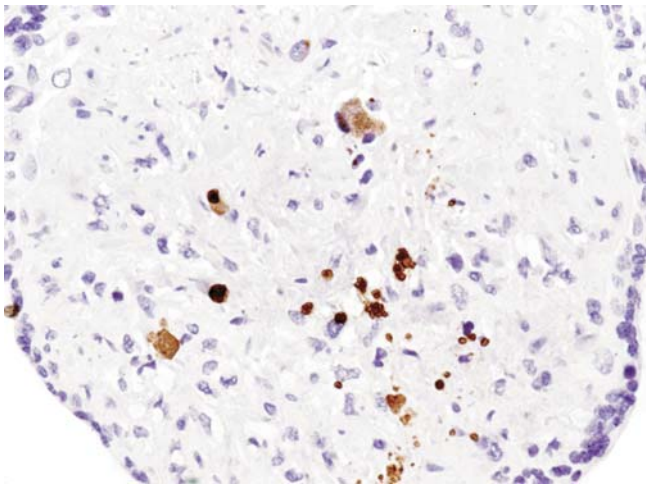

FIGURE 20.66. Villus in congenital toxoplasmosis, anti-toxoplasma antibody staining (brown).

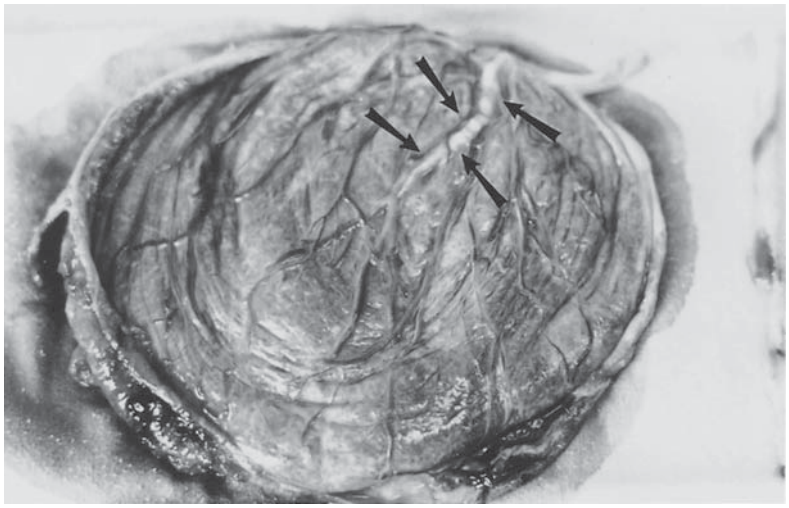

FIGURE 20.67. Placenta of a stillborn with hydranencephaly and other destructive features due to toxoplasmosis. Note the calcified venous thrombus at (arrows). (Courtesy of Dr. G. Khodr, San Antonio, Texas.)

from nine control specimens. Only 19 of the 23 patients had a positive serologic reaction. He isolated *Toxoplasma* from the brain of two successive abortuses. He also described another case with probable toxoplasmosis. In several cases, however, he required several passages for identification, an important aspect of his work.

Garcia (1968) observed a similar patient. This woman delivered a severely affected child who died within a day. Aside from many areas of typical destruction, organisms were shown to exist in several organs. The placenta had many cysts and villitis with conglutination of villi. Cysts were also found around the umbilical vein. A second pregnancy ended with a macerated abortus, also with typical histopathologic changes. Again, *Toxoplasma* organisms were identified; they were also present within the decidua, but they were much less well depicted there. Thus, some doubt of recurrent disease lingers. The suspicions that transplacental toxoplasma transmission may be enhanced in HIV-infected patients have not been supported by the study of Minkoff et al. (1997).

Kala-Azar

This visceral leishmaniasis is due to *Leishmania major* infection. It is endemic in parts of Africa, and placentas from infected pregnancies have rarely been observed, even though congenital infection is known to occur occasionally. Eltoum et al. (1992) described such a case, a 5 months abortus, as well as a transplacental infection. In the placenta of the abortus, numerous villous vessels were thrombosed and contained typical organisms, amastigotes, within and outside of macrophages. The organisms were confirmed by electron microscopy. There was no inflammation and only focal trophoblastic degeneration was observed.

Chagas' Disease

Chagas' disease (American trypanosomiasis) is caused by infection with *Trypanosoma cruzi*, an organism that is transmitted by the bite of an infected triatomid, the "kissing bug." The disease is largely limited to Brazil, Paraguay, Chile, and Argentina, but rare cases (also of organism and vector) have come from Mexico and the United States (Woody & Woody, 1974). Chagas' disease produces a wide variety of symptoms and is characterized by a frequently long latent period. Best known are myocarditis and esophagitis, but encephalitis, hepatosplenomegaly, and many other manifestations are well recorded. It is an important and frequent disease in northeastern Brazil. The disease is also known in Venezuela, from which the first congenitally acquired cases were described (Gavaller, 1953). Since then, numerous instances of congenital Chagas' disease have been published. Most have been from Salvador (Bahia, Brazil), but a mild transplacental infection in a Mexican patient was detailed by Gilson et al. (1995). The latter authors pointed out that with currently greater mobility of people, the infection should be more commonly suspected.

The extensive Brazilian literature on congenital and placental Chagas' disease has been reviewed in English by Bittencourt (1976), who is the major contributor to our knowledge of this disease in newborns. Her paper also described in detail the placental pathology. The (maternal) disease was often first identified by the autopsy of stillborn infants, whose organs contained large numbers of the organisms. When parasitemia exists in the mother, the trypanosomes gain access from the intervillous space by traversing the trophoblast as trypomastigotes. This step may occur during an acute infection but is most common in the chronic phase of the disease. In the villi, the organisms change character, becoming amastigotes, and remain

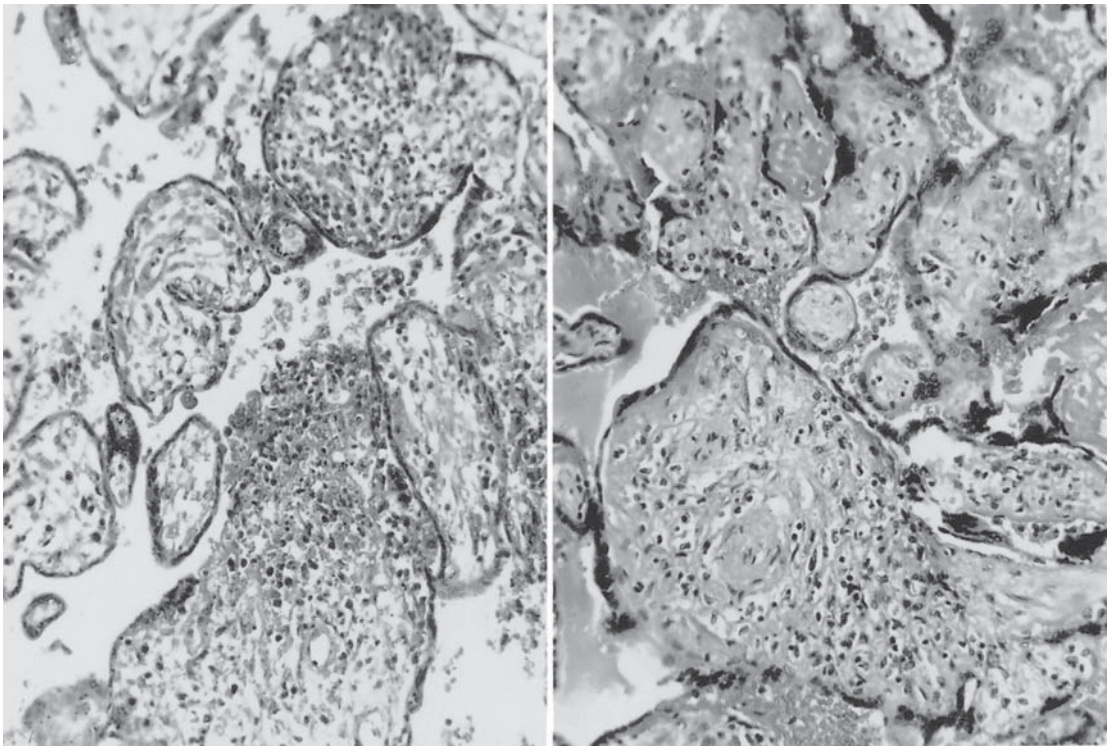

FIGURE 20.68. Chronic, destructive villitis due to Chagas' disease. Although many organisms are present, they cannot be seen at this magnification. The villi at top right are agglutinated; they have long been fibrosed and are functionless. H&E ×250. (Courtesy of Dr. Achiléa Lisboa Bittencourt, Bahia, Brazil.)

phagocytosed by Hofbauer cells. When they are released from these cells, they enter the fetal circulation as trypomastigotes. Not all placentas with Hofbauer cell infection cause congenital disease in the fetus. Most of the placentas studied by Bittencourt showed a massive parasitic load, chronic destructive villitis, and intervillous accumulation of fibrin and inflammatory cells (Fig. 20.68). Fibrosis and an occasional villous granuloma-like reaction were also seen. The amnionic epithelium and Hofbauer cells were the commonest place for amastigotes to be located, although in one case a massive accumulation was found in the syncytium (Fig. 20.69). In a later contribution, Bittencourt et al. (1981) beautifully depicted the amnionic amastigote infection, and showed that the umbilical cord also had surface and internal amastigote aggregates; she speculated that an important route of amnionic epithelial infection may be from infected fetal lung. The chorion also occasionally contained organisms.

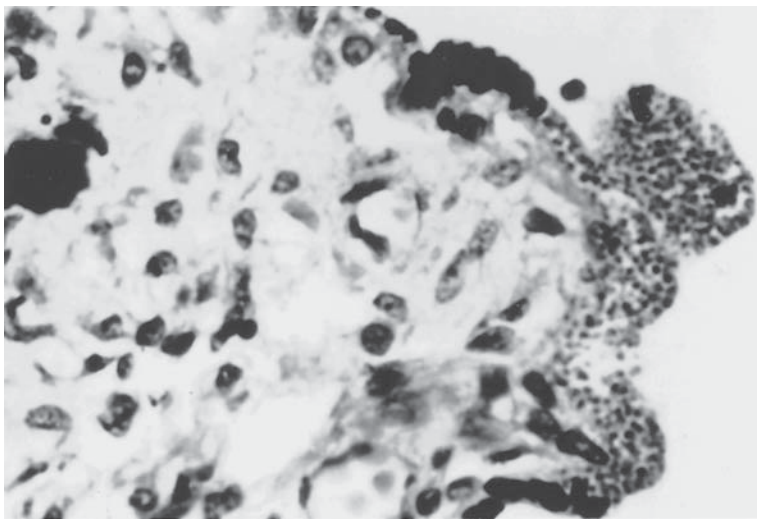

FIGURE 20.69. Placenta of a mother with Chagas' disease, showing amastigotes in the syncytiotrophoblast. This newborn was without overt disease, even though the placenta was infected during the acute phase of the maternal disease. H&E ×400. (Courtesy of Dr. Achiléa Lisboa Bittencourt, Bahia, Brazil.)

The placentas of many affected fetuses were markedly enlarged, pale, and disrupted. Drut and Araujo (2000) depicted unusually large cells in villous stroma and determined their hyperdiploid DNA content. Mezzano et al. (2005) described reduced expression of placental alkaline phosphatase in infected and in diabetic placentas and suggested a causal relation with the presence of trypanosomes in trophoblast. Perhaps, so they speculated, diabetic patients may be more susceptible. Mjihdi et al. (2002) induced placental and fetal lesions in experimental studies of mice using this organism, and Shippey et al. (2005) used trophoblast cell cultures and perfused cotyledons to investigate early infection with trypanosomes. The former mode of infection was more successful.

BABESIOSIS, TRICHOMONIASIS, RICKETTSIA, AND EHRLICHIA

Transplacental **babesiosis** has been described, but the placenta was not studied (Esernio-Jenssen et al., 1987). The mother had been bitten by a tick 1 week before delivery; the infant was treated successfully. The organism, *Babesia microti*, was identified in 5% of the child's red blood cells.

Trichomoniasis of the vagina, caused by *Trichomonas vaginalis*, frequently complicates pregnancy and is the most common sexually transmitted disease according to Stine (1993), and it has been suggested that it is a cause of premature delivery, especially because it may be associated with bacterial vaginosis (James et al., 1992; Cotch et al., 1997; Boon et al., 2002). Mason and Brown (1980), who studied 70 infected parturients and a control group of patients, found that there was no relation of premature delivery and vaginal trichomoniasis. Cotch et al. (1997) examined a large population of women. They ascertained that vaginal trichomoniasis in the middle trimester is associated with preterm delivery and low birth weight. They corrected for associated infections but were unable to correlate PROM with this trichomoniasis. These authors and Graves and Gardner (1993) considered the probable pathogenicity of this organism upon the endocervical canal and placental membranes. Neonatal infection of respiratory passages and pneumonia, presumably acquired at delivery, have been reported in a few newborns (Al-Salihi et al., 1974; McLaren et al., 1983; Smith et al., 2002; Hoffman et al., 2003). They were delivered vaginally; the placentas were not described. The organisms are difficult to identify histologically, and they would most likely be overlooked in routine examinations (see Lossick & Kent, 1991). Fetal and placental inflammatory lesions have been well delineated in bovine abortions due to a related flagellate (Rhyan et al., 1988), but detailed placental studies in humans have not been reported. They are desperately needed, as the light-microscopic examination of tissue sections is incapable of detecting this organism. Fortunately, new methods for identification have become available such as fluorescent DNA in situ hybridization (Muresu et al., 1994), and the sequence of the trichomonas adhesive protein has been identified (Rappelli et al., 1995). But it needs to be reemphasized that trichomoniasis is one of the most common (if not the most common) sexually transmitted diseases, and it has major sequelae that are in need of more decisive study (Soper, 2004).

Rickettsial disease (Rocky Mountain spotted fever) occurred during the pregnancy of a patient described by Markley et al. (1998). After chloramphenicol therapy the patient recovered; the placenta and infant were normal.

Ehrlichiosis is an infection with placental transmission identified in horses (Long et al., 1995). The infection causes abortion in sheep, cattle, and horses, and several different species of organisms have been delineated. There is one report of neonatal infection in humans, by Horowitz et al. (1998). The mother was infected, living in a tick-infested environment, and responded to doxycycline therapy. The neonate became clinically ill at age 7 days and had massive infection of granulocytes with the agent referred to as "human granulocytic ehrlichiosis." The placenta had not been examined, but circumstances suggested to the authors a prenatal, transplacental infection.

Malaria

Infection with one of the four species of malaria plasmodia is the commonest infectious disease in the world, but truly congenital infection has been described only rarely. Naeye (1988b) made the point that it is important to differentiate between malaria in endemic regions and malaria in areas where the disease is sporadic. The former have continuously new antigen presentation and different, enhanced immune reactions. He believed that this point may be important in the outcome of the disease and its possible transmission to the fetus. But the mechanism of fetal/neonatal infection is still uncertain, despite the prevalence of malaria.

Most authors have found that pregnancy substantially increases the severity of malaria. The disease is associated with premature births, and it reduces the weight of the fetus and placenta (references in Bruce-Chwatt, 1966; Wyler, 1983). There is also some evidence that malaria-infected erythrocytes may be "sequestered" in the intervillous space of pregnant patients (Bray & Sinden, 1979). This sequestration was explained by the expression of intercellular adhesion molecule-1 (ICAM-1) on monocytes in "chronic malaria infection" (Sugiyama et al., 2001). Muthusamy et al. (2004) showed that infected red cells adhere to trophoblast by a "low-sulfated chondroitin sulfate proteoglycan receptor." This attachment, so Crocker et al. (2004) suggested, leads to syncytiotrophoblastic degeneration, possibly thus relating to deficient fetal growth (see Nosten et al., 1999). The organisms have often been identified in the blood of the intervillous space (e.g., Jelliffe, 1968) and may be retained there because of the "sequestration" even after apparently adequate therapy (Procop et al., 2001). It is also stated that the placenta may be "diagnostically black at parturition" owing to malaria pigment (Anonymous, 1983c). This pigment ("haemozoin") has been quantitated by Sullivan et al. (2000), but its quantity was unrelated to fetal outcome. In a study that used polarization microscopy, Romagosa et al. (2004) have shown that this modality is superior in detecting the parasites, as well as the pigment, so long as the tissues were fixed in buffered formalin. Mount et al. (2004) showed that the impairment of humoral immunity to malaria surface antigens in pregnancy is occasionally the result of HIV infection, thus explaining the enhanced susceptibility in pregnancy to malaria.

Congenital infection with malarial organisms occurred in only one twin reported by Tanner and Hewlett (1935) and Balabat et al. (1995). The latter authors asserted that only 300 cases of congenital malaria have been described, and only five were in twin pregnancies. They also suggested that transplacental infection occurred most likely during delivery. Following an epidemic, Wickramasuriya (1935) described six cases of congenital malaria. He believed that congenital infection is much more common than was believed prior to his report. It included a review of previous statements that denied or assumed congenital infection to occur. The patients in his study were severely infected, and several died undelivered with fetus in utero. Parasites were found in umbilical cord blood of one patient, and in the brain and spleen of two. Five fetuses had malaria-pigmented spleens, and one placenta had many infarcts and an abruptio. Other reports of congenital malaria have been reviewed in case reports by Woods et al. (1974) and Thompson et al. (1977). A frequently cited report of Quinn et al. (1982) described four children who had their first febrile episode at 3 to 4 weeks of age. Their mothers had come to Seattle, Washington, from abroad, and the new infection is unlikely to have occurred in Seattle. The mothers had been febrile during labor or before; the placentas were not studied, and the mechanism of fetal infection is only surmised. It was suggested that perhaps antibodies or other proteins suppressed fever before the children finally became ill. In general, perhaps because of transferred immunity, symptomatic disease becomes evident only after several weeks in the neonate, as in the four infants just described. The disease is virtually never recognized at birth or it may be very difficult to diagnose (Hewson et al., 2003). That the transmission was prenatal (or occurred during delivery) in some of these cases is evidenced by reports of neonatal malaria in patients returning from abroad to the United States and delivering their infants here. Organisms have definitively identified in umbilical cord blood but is said to be more common when the fetus has had an opportunity to make IgM antibodies (Xi et al., 2003).

When it is stated in the literature, however, that the "placenta was infected," this usually refers to the demonstration of organisms in blood smears made from the placenta. Such organisms could have originated from the intervillous space, as was well demonstrated by the photograph in the studies by Miller and Telford (1997a,b) upon which Lane (1997) and Edwards (1997) commented. Histologic studies have usually not been done, or have been reported only infrequently. One such report, including ultrastructural study, came from Gabon (Walter et al., 1982). These investigators found placental parasites in smears from 33% of cases in an unselected population collected in an endemic area. Infected erythrocytes were frequent in the intervillous space, and there was an accumulation of associated macrophages (Fig. 20.70). An increased amount of intervillous fibrin was present; thickening of trophoblastic lamina was interpreted as possibly representing the results of an immune reaction. The authors suggested that syncytial damage may have occurred, and they found ample malaria pigment (a hemoglobin breakdown product) in fibrinoid, macrophages, and "free" in the intervillous space. In the authors' opinion, plasmodia cross the placenta infrequently, and in their study the event was not demonstrable. This opinion is different from that of Naeye (1988b), who quoted Reinhardt as having found parasites in the fetus as frequently as in 55% of cases.

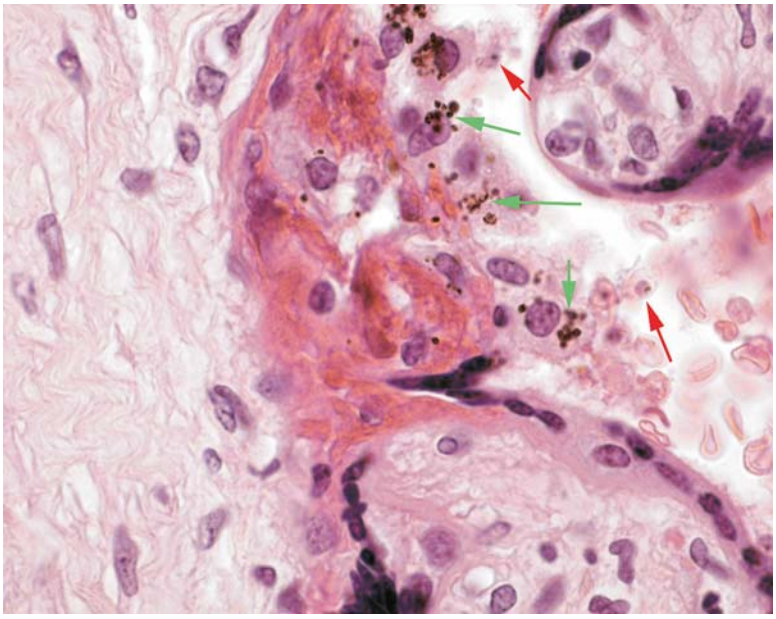

Figure 20.70. Malaria infected placenta with focus of syncytiotrophoblastic necrosis and pigment (hemozoin) at green arrows. Malaria parasites at red arrows.

The discrepancy is not resolved. The workers who have looked at the placentas histologically have not identified organisms in the fetal circulation. This is also our observation, based on studies of infected Vietnamese patients who have delivered at our hospital. Our present view is that the plasmodium does not cross by itself. When transplacental infection does occur, the parasites are probably transferred within red blood cells. Although maternal to fetal transfer of red blood cells is rare, it does occasionally happen (see Chapter 17). This concept accords with the original observations made by Wickramasuriya (1935) as well. He demonstrated organisms in some stillborns and in the umbilical cord blood of one fetus. His patients had unusually severe pregnancy complications, several having died before delivery. These complications may well have contributed to the enhanced transfer of infected red blood cells. Ordi et al. (1998) examined the placentas of a large cohort of patients in Tanzania and detected "massive chronic intervillositis" in 6.27% of their patients. Of 1179 placentas studied, 415 showed parasites as evidence of active infection, 475 had malaria pigment without parasites, 289 had no evidence of infection, and 74 had massive intervillositis. At least 75% of the intervillous space was involved with infiltration of mainly "monocytes and histiocytes" (CD68- and CD45-positive cells), and frequent fibrin deposits were also observed. Pigment was identified by polarized light study. Four cases had fetal vascular thromboses. The report has an extensive discussion of intervillositis of different origins, but fetal infection was not addressed by these authors (see also Chapter 21). The nature of the intervillous inflammatory cells was studied in greater detail by Ordi et al. (2001) in the same population. It was found that natural killer (NK) cells are conspicuously absent among the cells. Nebuloni et al. (2001) commented on this observation and presented a malaria patient with massive "intervillositis" (vide infra) and further identified the cell type (CD68, CD45RO–, few CD20+).

Coxiella burnetii is the organism that causes Q-fever, a zoonosis commonly contracted from domestic animals. Congenital infection with intrauterine fetal death was reported by Friedland et al. (1994). The placenta had a 40% involvement with severe necrotizing villitis with many organisms in the villi. Raoult and Stein (1994) reported another case and reviewed other cases from the abortion literature.

OTHER PARASITIC INFECTIONS

Kain and Keystone (1988) reported a patient with recurrent hydatid disease (*Echinococcus granulosus*) during pregnancy. A normal child was born; the placenta was not described. Invasion of the embryo by *Enterobius vermicularis* was described by Mendoza et al. (1987). They depicted a 2-cm embryo, with placenta, and showed the worm to reside within the abdomen of the embryo. The pregnancy was surgically aborted because of the presence of a dead embryo. There was no inflammatory reaction in the embryo or placenta. When Cort (1921) reviewed the topic of fetal worm infestation, he found only indisputable evidence for transmission of **hookworm** and *Schistosoma japonicum*. In dogs, sheep, and other animals, prenatal transmission of lung worm is well known. Sutherland et al. (1965) depicted placental infection with *Schistosoma haematobium* from a normal delivery. The organisms were located within decidua and villi, but no inflammatory reaction was described. In an addendum, additional cases were discovered. Several other references were made to a case of placental infection with different species of schistosomes. Thus, Bittencourt et al. (1980) found placental infection with *Schistosoma mansoni* in four cases. The gross morphology of the placenta showed no characteristic features, but microscopically granulomas around Schistosome eggs were present in fibrin and villi; occasional worms were also present and are illustrated. Although all four fetuses died, they had no evidence of infection by the worms. Presumably the rarity of this description relates to the paucity of placental studies. Pregnant women also suffer occasionally from disseminated **strongolydiasis**, but we are not aware of a report of placental pathology in this disease.

Villitis of Unknown Etiology

Chronic villitis occurs frequently. Rüschoff et al. (1985) found it in 6.6% of 1240 placentas studied, whereas Altshuler (personal communication, 1993) estimated a frequency of 5% to 10% in consecutive placentas. Labarrere et al. (1989, 1990), who referred to it as "villitis of unestablished origin" reviewed the incidence and found it to vary in studies from 6% to 33.8%. Villitis of unknown etiology (VUE) is especially frequent in the villi that are near the maternal floor of the placenta, and we have found it to be more commonly in placenta accreta at the implantation site (Fig. 20.71). At times, the etiology is apparent from the history (rubella) or the pathologic features (CMV infection). At other times, despite much effort, no specific etiology is elicited, often even when there are severe clinical abnormalities and autopsies are performed on the neonate. The entity has been termed **villitis of unknown etiology** since its original description (Gershon & Strauss, 1961; Benirschke & Altshuler, 1971; Altshuler, 1973c) and is now a well-recognized entity for placental pathologists. It remains a significant challenge to perinatal pathologists because of its frequency, its high recurrence rate, and the associated poor pregnancy outcome. Sporadic cases such as one we saw with maternal granulomatous disease do not assure a causal relation. No conclusive information on the etiology of VUE has been gained since it was first mentioned by Gershon and Strauss (1961). It is unfortunate that these authors misused the term *placental insufficiency* in this context, a designation to which we do not subscribe. In the literal sense, that term should be used only to represent a pathophysiologic state; it is not synonymous with specific morphologic abnormalities. In our view, few other well-defined lesions of the placenta exist (e.g., maternal floor infarct) for which a fetal or maternal cause cannot be assigned; the term *placental insufficiency* subtly implies that there

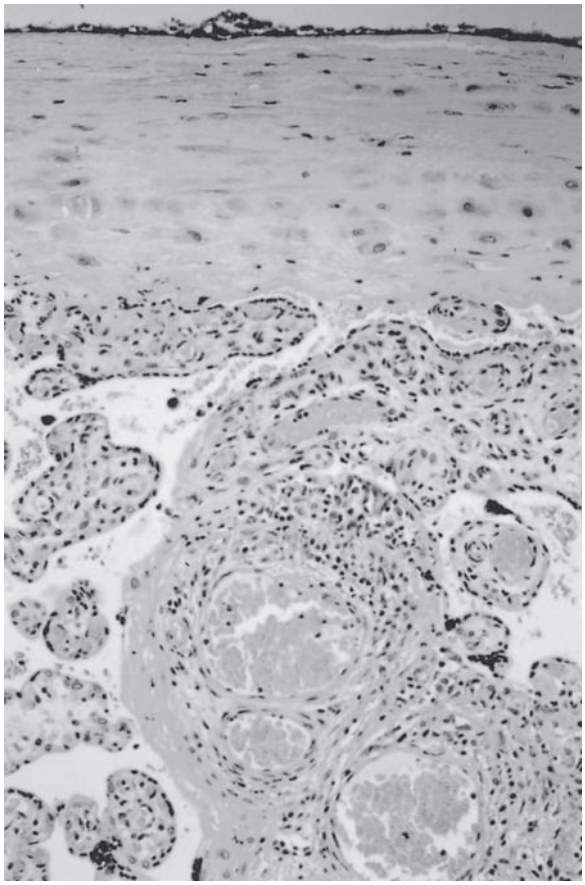

FIGURE 20.71. Focal villitis of unknown etiology (VUE) in anchoring villi at implantation site of a placenta percreta. The villi are attached to the connective tissue scar of previous cesarean section. H&E ×160.

is an intrinsic defect in placental function or its development. We believe the concept of placental insufficiency to be misleading and one that diverts attention from the search of pathogenetic mechanisms.

The pathologic findings of VUE have often been depicted since the initial emphasis on this entity's recognition (Benirschke & Altshuler, 1971), but there is evidence that the interpathologist diagnostic error of this diagnosis is considerable (Khong et al., 1993). The constituent lesions have a wide spectrum, from occasional villous involvement to extreme involvement wherein all villi have some pathologic reaction (Russell, 1980). Altshuler (1973c, 1984) summarized the salient features of VUE as follows: proliferative villitis; necrotizing villitis; granulomatous, cicatricial, reparative, evanescent villitis; fetal vasculopathy; avascular villi; placental dysmaturity; increase in nucleated red blood cells; hemosiderin; hemorrhagic vasculitis; necrotizing deciduitis; basal villitis; chorangiosis; and ischemia or infarction. All of these abnormalities may be found in cases of placental VUE, or only some of them may be present.

The similarity to known infectious causes of villitis, such as seen with CMV and rubella, is striking. Even though no infectious cause has been delineated for VUE, this entity is discussed here because of its presumed relation to congenital infection. It may well be proved in the future that VUE is not a single or uniform lesion, independent of host immune factors, but that it is composed of several etiologically distinct variants. It is a challenge for future investigation that has recently been taken up by several investigators.

One should also note that degenerative lesions, somewhat simulating VUE, occur peripheral to infarcts (subinfarctive villous degenerations). These lesions are not to be confused with typical VUE as here discussed. VUE is often associated with fetal growth restriction. Altshuler (1984) saw it in 33% of such cases, Dollmann and Schmitz-Moormann (1972) described it in their patient with recurrent abortions, and others found similar effects (Russell et al., 1980; Labarrere et al., 1982; Salafia et al., 1988). Rüschoff et al. (1985) described the placentas of VUE as "stiff," but a specific macroscopic delineation of VUE has not yet been possible. The placentas are occasionally smaller and have more fibrin content, but no other change allows macroscopic identification.

The frequency of VUE varies with the nature of the investigation, that is, the selection of the material. In general, one may expect VUE in approximately 5% to 8% of consecutively studied placentas. When those of complicated pregnancies, growth-restricted infants, or fetal deaths are studied, the incidence is much higher.

There is little doubt that VUE eliminates a considerable amount of placental parenchyma from nutrient transfer. Fetal growth restriction is thus not surprising. One must emphasize, however, that there is no absolute relation between the severity of VUE and the severity of fetal growth restriction. Attempts to show a relation to elevated fetal IgM levels have not been successful (Mortimer et al., 1985), nor have numerous attempts to identify specific organisms with a variety of serologic, cultural, or structural tools. When neonates survive even severe VUE, they have no detectable illness, and those who die show no lesions at autopsy.

Of greatest interest to us is the frequently recurrent nature of this lesion, so well described in the contribution by Dollmann and Schmitz-Moormann (1972). They saw a patient with two growth-restricted infants followed by three abortions, all with VUE as probable cause. They found that, in some instances, there was a marked intervillous accumulation of macrophages (intervillositis). These cells they determined to be of maternal origin, whereas most of the intravillous inflammatory cells could not be typed with sex chromatin but were thought to be of fetal origin. Jacques and Qureshi (1993) observed six cases of chronic intervillositis and determined the cells to be primarily histiocytes. They were unable to rule out

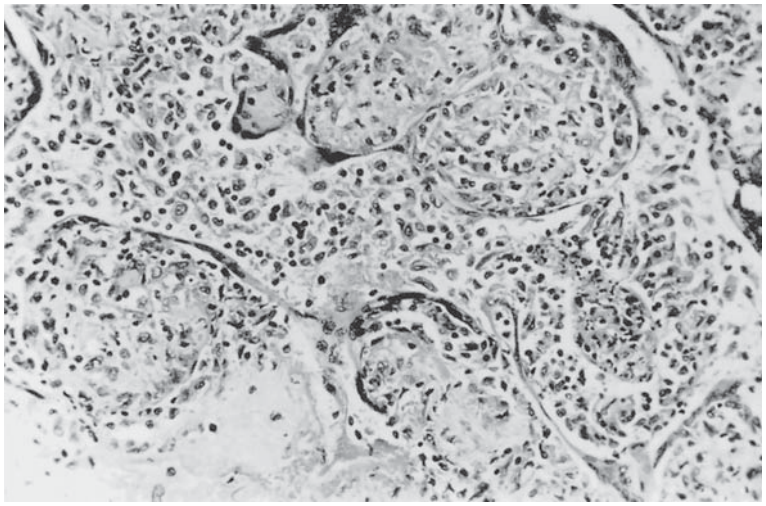

FIGURE 20.72. Placenta of 36 weeks' gestation stillborn with VUE. It was the second of three successive such events. Note the intense intervillositis with histiocytes and lymphocytes, villous infiltration, villous necroses, and vascular obliteration. H&E ×250.

infection, found an association with increased fibrin deposition, and identified some other pathologic features. Although the lesion had a poor prognosis, they were unable to define it more precisely or to identify an etiology. They favored an immunologic determination and next examined it in twin gestations (1994), as did Doss et al. (1995), who suggested a relation to recurrent abortion (see Chapter 21). Discordant involvement of twins was found in both DZ as well as MZ twins, and growth restriction was associated, as was also the case in Kaplan's description (2003) of a set of discordant MZ twins. They pointed out that both viral and immunologic hypotheses for the etiology of VUE are difficult to support when VUE affects the placental portion of only one of monochorionic MZ twins. The suggestion relating to VUE and for the adherence and possible penetration of maternal lymphocytes/monocytes to syncytial cells comes from the in vitro studies by Xiao et al. (1997). They showed that inflammatory cytokines of various types increases the avidity of monocyte-binding to syncytium through activation of surface ICAM-1. An immunologic pathogenesis of VUE with maternal cells infiltrating the villi has long been championed by Labarrere and his colleagues (1991). They had earlier first characterized the lesion of chronic intervillositis (Labarrere & Mullen, 1987) and now demonstrated the presence of tissue factor (an initiator of thrombosis through activation of factor VII) in normal villous stroma. In VUE, one often finds minor thromboses in villous capillaries and larger stem vessels. These investigators assume that these originated secondary to focal inflammation, thus releasing cytokines from locally activated helper T cells and macrophages. They envisaged that such reaction would locally engender thrombosis. Further discussion of intervillositis is to be found at the end of this section.

Another of the few attempts at determining the precise nature of the inflammatory cells in villitis is that of Hartwick et al. (1989) in a case of fetal parvovirus B19 infection. They found the cells to have a T-cell derivation and provided some support for the fetal origin in this admittedly different disease. Although most of the inflammation in VUE is apparently histiocytic/lymphocytic, plasma cells (B-cell derived) occur as well but much less commonly. We have reason to believe that, in CMV infection, the plasma cells are fetal in origin. Histologic considerations had led us also to believe that in many cases the inflammatory cells of VUE are of fetal origin, but recent studies now indicate that in many instances the majority of the infiltrating cells are maternal cells. In addition, it is apparent that frequently the major inflammatory component is located within the anchoring villi. Also, they are often associated with maternal plasma cell infiltration of the decidua basalis. Indeed, chronic villitis may be *limited* to anchoring villi. Here, the cellular components have a maternal origin, and a dual derivation of the histiocytes, therefore, cannot be excluded. Labarrere et al. (1982) and Russell (1980) have also emphasized the frequent decidual involvement with lymphocytic inflammation and have suggested that VUE may have a relation to chronic endometritis. Whether the recurrent VUE in a patient with recurrent herpes gestationis described by Baxi et al. (1991) has a causal relation will remain unknown until more cases are studied.

The possibility of chronic brucellosis was entertained in a patient of ours with three consecutive pregnancy failures and histologic VUE (Figs. 20.72 and 20.73). Detailed study, however, was negative. In a later pregnancy, the progress was monitored with estriol levels, and when they declined, an elective cesarean section was performed. The growth-restricted infant did well and has remained healthy during the 15 years since this occurrence. The placenta was so severely involved with villitis that one wonders how this infant could have been born alive (Figs. 20.74 and 20.75). The lesion of the first preg-

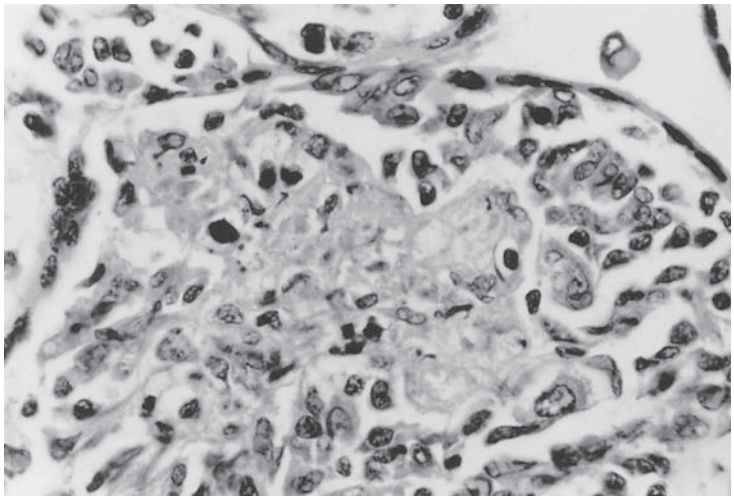

FIGURE 20.73. Same case of VUE as in Figure 20.72. The villous destruction and cellular infiltration are pronounced; occasional plasma cells are present. H&E ×640.

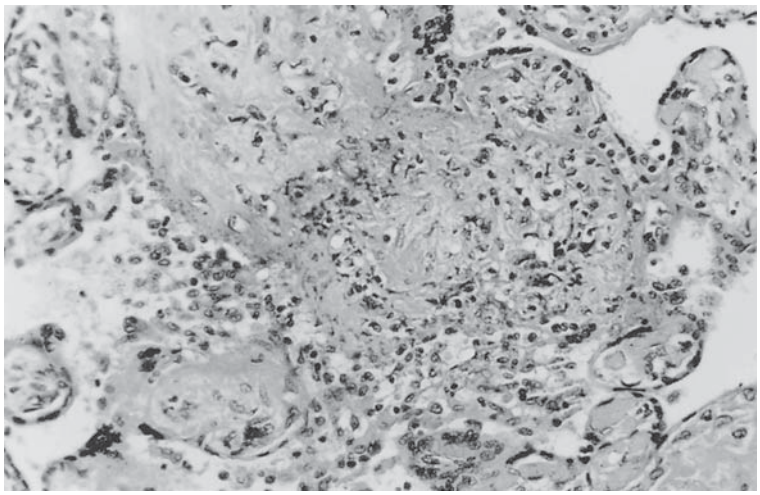

FIGURE 20.74. Placenta of the third pregnancy of a patient with recurrent losses and VUE (as in Figs. 20.72 and 20.73). Patient was also hypothyroid and on medication for this problem. When the amnionic fluid lecithin/sphingomyelin (L/S) ratio became more than 3:1, a cesarean section was done producing a viable fetus. Ten years later, the infant was well. Despite the extensive necrosis and inflammation, this infant weighed 2500 g at 37 weeks. The placenta was 510 g and had massive VUE with destruction of villi and trophoblast. H&E ×250.

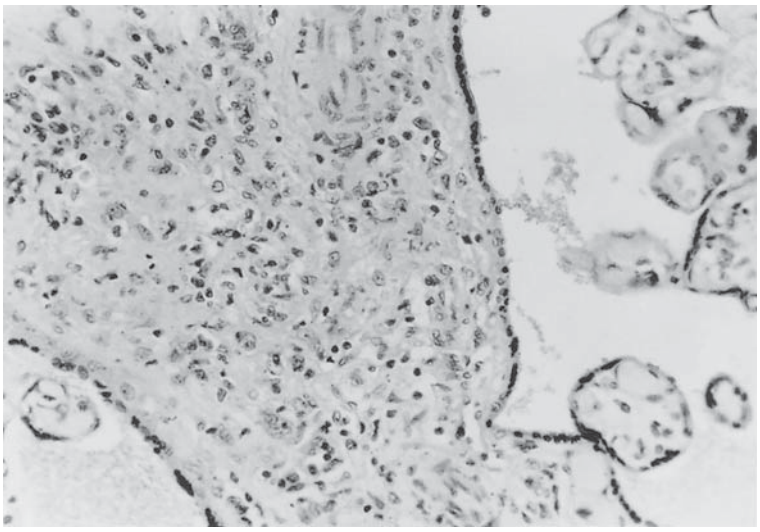

FIGURE 20.75. Same case as in Figure 20.74. Note the degeneration of the villous vessels. There is no trophoblast necrosis at this site, so the inflammatory cells are likely of fetal origin. H&E ×250.

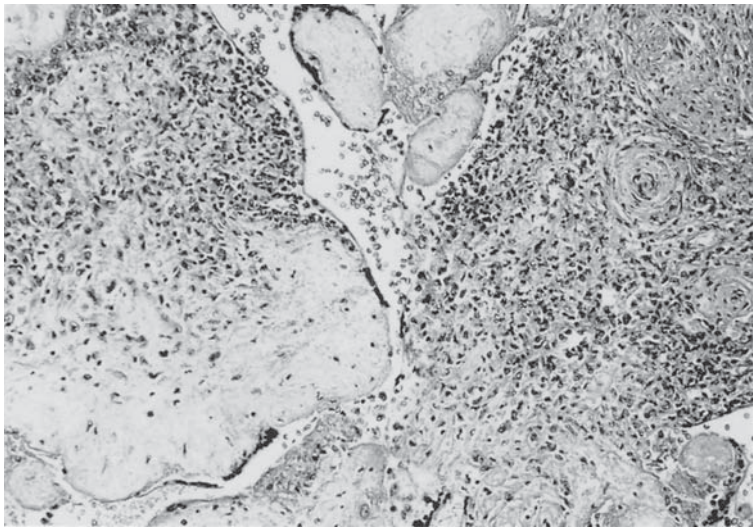

FIGURE 20.76. This placenta comes from the first stillborn (at 37 weeks' gestation) of the patient with recurrent VUE (Figs. 20.72–20.75). There is even more necrosis and inflammation of villi than in the other pregnancies depicted. H&E ×100.

nancy was identical (Fig. 20.76). The severity and destructive nature of VUE is further exemplified in Figure 20.77, a stillborn, growth-restricted fetus. In yet another case, it was our opinion that the increased frequency of late decelerations during monitoring was caused by the placental lesions shown in Figure 20.78 (Benirschke, 1975). These inexplicable areas of villitis were scattered throughout the placenta. In the case of a severely compromised newborn, the placenta had many vascular occlusions and surface thrombi (Figs. 20.79 to 20.82). No virus infection was diagnosed. This picture is substantially different from the hemorrhagic endovasculitis (HEV) of Sander et al. (1986), which was discussed in Chapter 13.

The precise etiology of VUE is thus still unknown. In fact, we do not even know whether this is a uniform disease or one that, when it is better understood, falls into several etiologic categories. Altshuler and Hyde (1996) drew attention to the possible interaction of cytokines and ensuing fetal growth restriction. Infants can, however, survive even severe placental villitis without showing subsequent impairment. Their long-term outcome requires much additional investigation. Three principal suggestions have been made with respect to the possible etiology of VUE:

1. It is an infectious (perhaps viral) disease, and due to an as yet unrecognized agent. That this concept has merit derives from the great histologic similarity of VUE to rubella and other known virus disorders that affect the placenta. Moreover, the discovery of parvovirus B19 infection and the similarity of placental response suggest that a viral agent must be sought in future studies. Furthermore, some of the common RNA viruses (Coxsackie, ECHO) are extremely difficult to recognize histologically or by electron microscopy. They also may cause few symptoms in the mother and may not be detected. The report by Garcia et al. (1991) brings this possibility into focus as well.

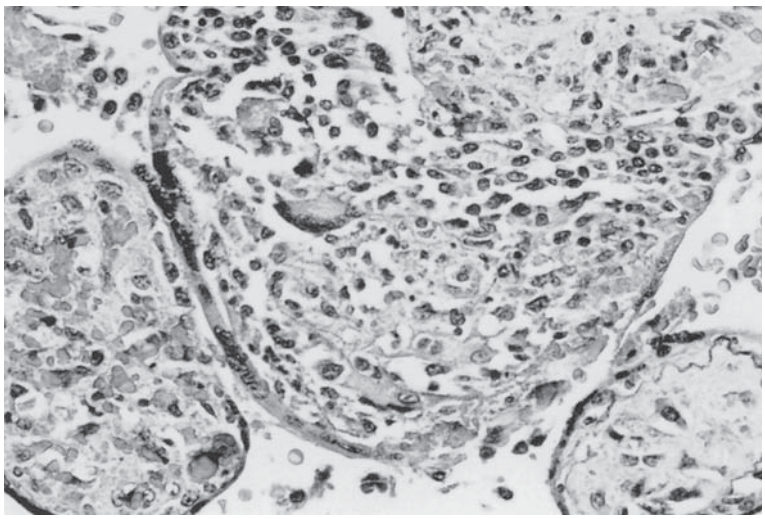

FIGURE 20.77. Villitis of unknown etiology in a stillborn fetus. The intense infiltration with lymphocytes, plasma cells, and histiocytes is widespread. Mineralization of the villous basement membrane is seen at bottom right. Several histiocytic giant cells are present in the central villus, whose trophoblast is degenerating focally. Vessels are obliterated. H&E ×640.

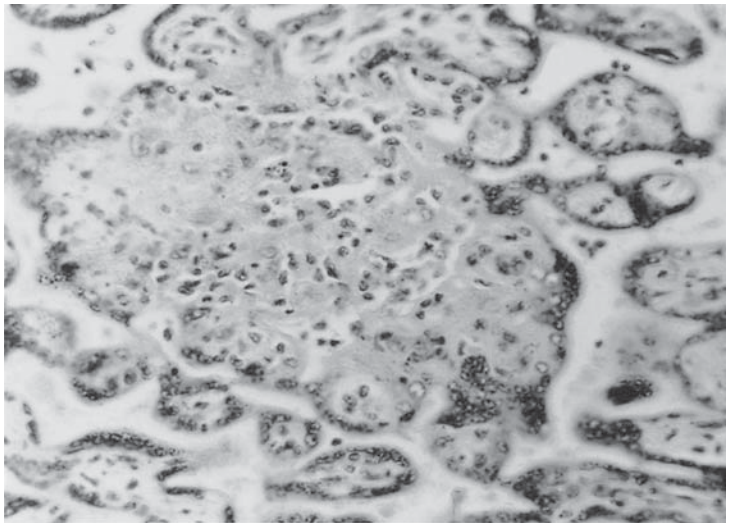

FIGURE 20.78. Mild chronic villitis in a 39-week pregnancy with good outcome. Late decelerations during labor were believed to be secondary to VUE. H&E ×250.

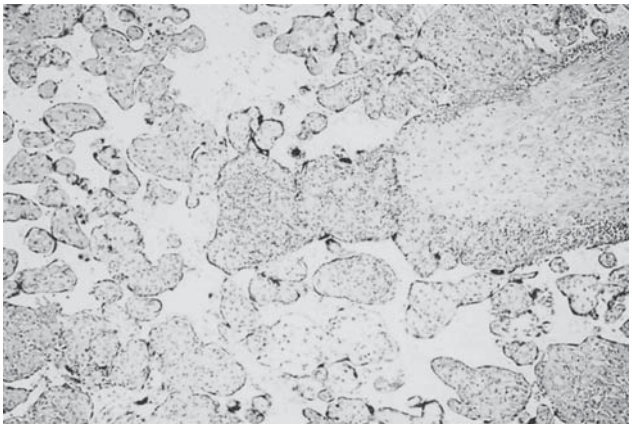

FIGURE 20.79. Severe chronic villitis in a premature infant with meconium aspiration. Extensive areas of villous destruction and inflammation are seen. H&E ×64.

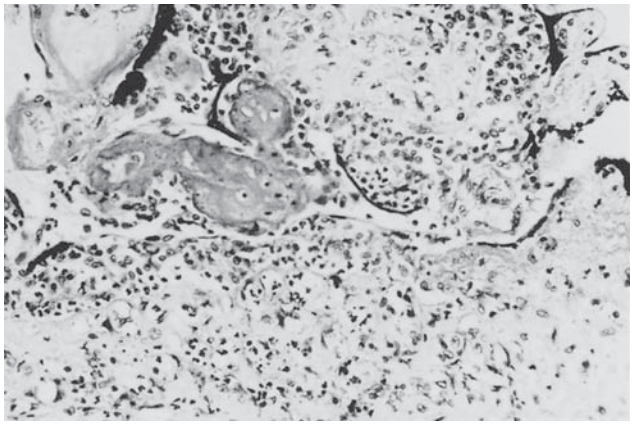

FIGURE 20.80. Same case as in Figure 20.79, showing the subtrophoblastic accumulation of lymphocytic infiltrate and villous necrosis. There were also chorionic vessel thrombi in this placenta. CMV and herpes infections were ruled out. H&E ×250.

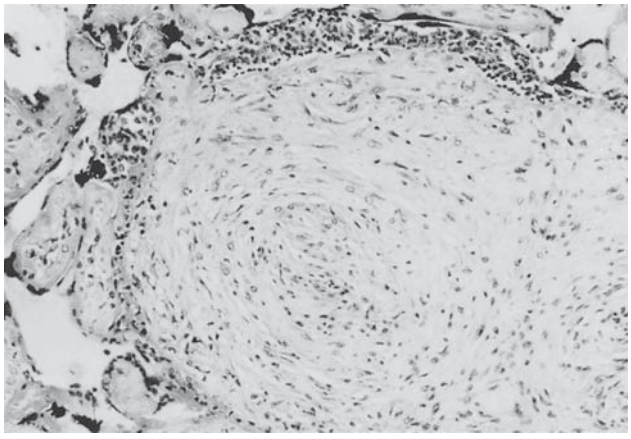

FIGURE 20.81. Same case as in Figures 20.79 and 20.80, again showing subtrophoblastic inflammatory cells and obliteration of villous stem vessel. H&E ×640.

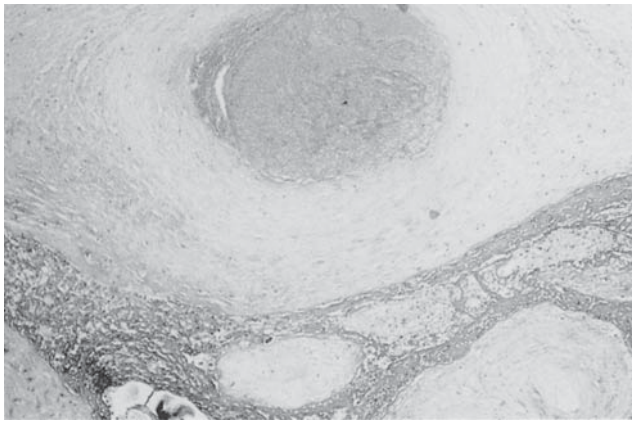

FIGURE 20.82. Same case as in Figures 20.79 to 20.81, showing an old thrombosis of a chorionic surface vessel in VUE. H&E ×64.

2. It is an immune reaction akin to placental "rejection" or even the graft-versus-host disease. Several investigators have raised this possibility, in particular because of the histiocytic predominance of the inflammatory reaction and the frequently recurrent episodes. At present, no new studies have conclusively shown or rejected this possibility. It is necessary to have more information on the "normal" fetomaternal immune interactions before this hypothesis can be rejected or affirmed. Moreover, professional immunologists need to be encouraged to become involved in the study of putative fetal antigen recognition. Redline and Abramowsky (1984) have commented on the possibility of the immune hypothesis. They found a 60% reproductive loss in patients with recurrent chronic villitis in contrast to a 37% loss in nonrecurrent villitis (Redline & Abramovsky, 1985). They suggested that VUE is much more common than heretofore believed; perhaps as many as 4% to 10% of placentas have some degree of VUE. They also suggested that "immunologic and structural abnormalities (uterine) in the host may play a role in its pathogenesis." Several of their patients had autoimmune diseases. Redline and Patterson (1993) found, with X-specific markers in male conceptuses' placentas, that approximately 60% of the infiltrating immunocytes of VUE represent maternal CD3 positive T-cells that have infiltrated from the intervillous space. This has now been proven. In studies conducted with a male fetus who succumbed in utero from this placental alteration was studied by colleagues of ours. They were able to show the fetal cells to lack the Y-chromosome marker conclusively, whereas it was present in all other villous and trophoblastic cells. The infiltrating cells were T cells and macrophages by immunocytochemistry, and of female gender. The reason for this response is presently unknown but is speculated upon in the contribution by Redline and Patterson. Essentially similar findings were made in the study by Kapur et al. (2004) and they found that essentially similar infiltrates of maternal origin characterized VUE as well as syphilitic villitis. One of our recent cases of VUE that led to fetal demise was also solely due to maternal infiltrates, as shown by Y-marker study. Greco and colleagues (1992) had also investigated the nature of villous stromal cells in VUE, syphilis, and CMV infection with a battery of antibodies and in situ hybridization. They concluded that these infiltrating elements had often markedly different phenotypes and that this was somewhat dependent on the nature of the underlying disease. They expressed an inability to decide about a possible immune reaction portrayed by this villitis (e.g., maternal cell invasion), but pointed out that "the expression of certain cellular markers for villous stromal cells is identical in both CMV and nonspecific villitis." For a review on the topic of placental nonrejection, see Hunt (1998). Labarrere et al. (1991) have championed this concept for years, and much of their investigations are there summarized. From their evaluation of placentas derived from in vitro fertilizations, Styer et al. (2003) proposed that VUE is twice as common with donor eggs than native eggs and inferred an immunologic mechanism. This was confirmed more recently by Perni et al. (2005).

3. The disease has a relation to preeclampsia and infarcts. Most of the patients we have seen do not have signs of pregnancy toxemia, and the "villitis" that is associated with preeclampsia is different. It has much less inflammation and is mostly degenerative in nature and found adjacent to typical infarcts. Therefore, we prefer to reject this hypothesis.

Since the original description by Labarrere and Mullen (1987) that defined the entity, a large study of **chronic intervillositis** was undertaken by Boyd and Redline (2000). They studied 21 patients and showed it to be a major cause of IUGR, spontaneous abortion, and fetal death (77%). The recurrence rate was high (67%), and three patients were found to have fetal chromosomal errors. Moreover, there was much intervillous fibrin deposition and some placentas had infarcts. Autoimmune and allergic processes of different kinds were found in 52% of their patients. The cells composing this intervillous infiltrate were of the TH1-type response and included activated macrophages as well as a smattering of other cells. Although this condition is not very common, it does represent an important aspect of fetal demise and IUGR. The authors emphasized that malaria needs to be excluded, as was earlier suggested. This can only be done by careful search for intervillous erythrocytic parasites and hemozoin deposits. A representative example of chronic intervillositis is shown in Figures 20.83 to 20.85. The severely IUGR fetus of this gestation was stillborn at about 17 weeks' gestation and the mother had one earlier abortion and one normal child. There was excessive fibrin deposition in the entire placenta and massive infiltration of the intervillous space by macrophages (CD68 cells). There was no chronic villitis, however, and there was no significant X-cell proliferation as is seen in maternal floor infarction (MFI). The mother had no history or symptoms of autoimmune or allergic diseases. Interestingly, one large maternal vessel of the decidua basalis was thrombosed.

Chronic intervillositis and VUE are sometimes combined, but in our experience this is not really common and we consider the two histologic entities to be different. At this time, the only certain and common finding is that VUE is not the result of infection with common, known pathogens. No virus or other agent has been consistently identified. Moreover, the children who are born from such pregnancies, many of whom are small for gestational age (SGA), develop normally. The efforts of

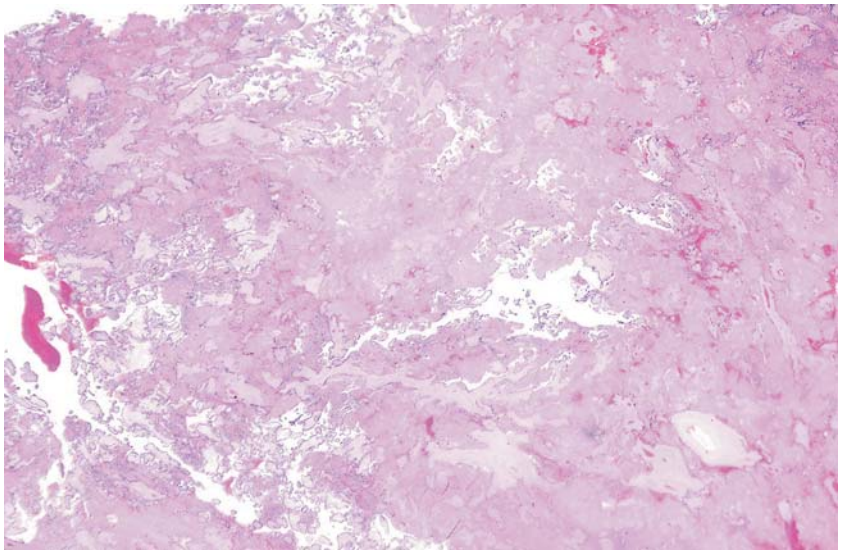

FIGURE 20.83. Low-power microphotograph of a typical case of chronic intervillositis. The entire placenta had this much fibrin deposition and collections of intervillous macrophages (dark blue). The intrauterine growth restriction (IUGR) fetus was stillborn but structurally normal.

several laboratories to identify the origin and nature of the inflammatory infiltrate suggest that a majority of the infiltrating cells is of maternal origin. Whether this is tantamount to an immune "rejection" phenomenon mounted by the mother against the placenta needs further investigation. The fact that the surviving infants of VUE placentas remain well and that the disease frequently recurs in families point in that direction. A recent comprehensive review of the frequency and relationship to IUGR and fetal demise has come from Becroft et al. (2005).

Likewise, chronic intervillositis has no definitive causal mechanism identified to date. It also may represent different end points of disease, such as malaria and maternal allergic conditions. Much more work is needed to unravel the complexity of these entities.

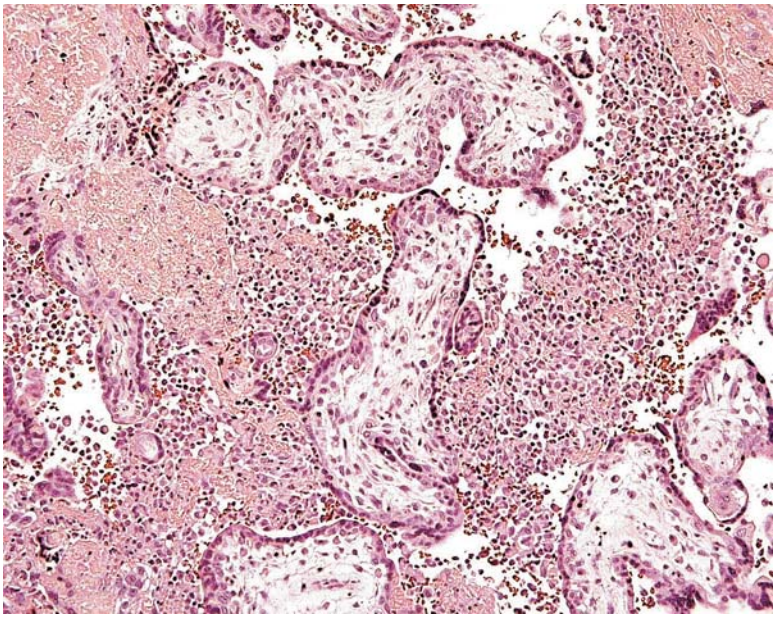

FIGURE 20.84. Chronic intervillositis at higher magnification with fibrin deposits and disuse infiltration of chronic inflammatory cells in the intervillous space.

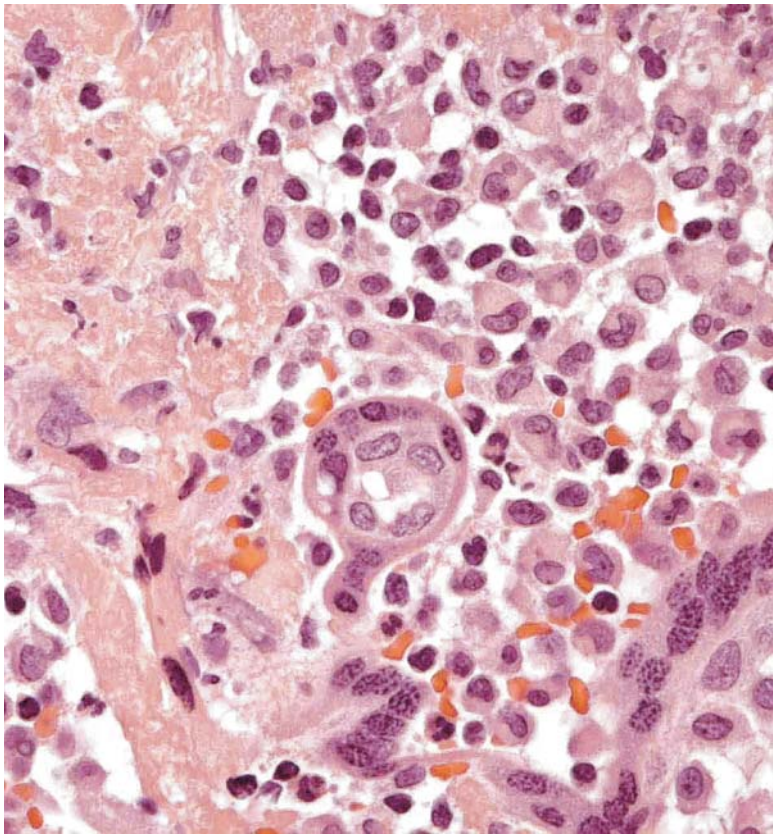

FIGURE 20.85. Still higher magnification of chronic intervillositis showing the chronic inflammatory cells (mostly activated macrophages), little villous erosion, and fibrin deposits.

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