Chapter 20

Placental Abnormalities in Fetal Conditions

Hydrops Fetalis

Hydrops fetalis is defined as severe, diffuse edema of the fetus. It has an overall incidence of 0.02–0.07% and is usually divided into immune and nonimmune hydrops. The majority of cases are nonimmune hydrops, the etiology of which is extremely varied. Nonimmune hydrops may be separated into the general categories of *congenital anomalies, infections, genetic disorders, hematologic disorders, fetomaternal hemorrhage, trauma, and miscellaneous*. Cardiac abnormalities are the most common, comprising approximately 40% of cases of nonimmune hydrops. About 35% of cases can be ascribed to genetic diseases; chromosomal anomalies make up 10–15%, hematologic disorders about 10%, and miscellaneous causes make up the remaining cases (Table 20.1).

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Immune Hydrops

Pathogenesis

Erythroblastosis fetalis, **hemolytic disease of the newborn**, or **immune hydrops** is a condition caused by *maternal antibodies directed against fetal red blood cell antigens*. The antibodies form due to "sensitization" from previous exposure to the antigen, usually from a previous pregnancy. These antibodies cause destruction of fetal red blood cells with resultant severe fetal anemia. In the majority of cases, the antibodies are directed against Rh-(D) antigens, but cases directed against other Rh antigens occur and unusual cases of sensitization against other antigens such as Kell or ABO have been described. Since immunoglobulin G (IgG) antibodies and not IgM antibodies are able to cross into the placenta, antigens that result in IgG antibodies are the most likely to result in disease. Hemolytic disease due to other antibodies does not differ *histopathologically* from anti-D-caused erythroblastosis, but clinical disease due to ABO-incompatibility and many other blood groups tends to be mild compared to Rh disease. Fetal hemolysis may rarely result from *glucose-6-phosphate dehydrogenase (G-6-PD) deficiency or virus infections* and it is important to differentiate these causes for the purposes of prognosis and treatment. As Rhogam prophylaxis has become more widespread, Rh incompatibility disease has become relatively uncommon in the United States, except in immigrant patients.

In typical erythroblastosis, there is transplacental transfer of maternal Rh antibodies leading to hemolysis in the fetus. The fetus attempts to replace this loss of red blood cells by overproduction and premature dissemination of immature red cell precursors [nucleated red blood cells (NRBCs)]. Fetal hematopoiesis becomes increasingly activated, and the peripheral blood thus contains a markedly increased number of **NRBCs** and **erythroblasts**. Over time, the severe anemia leads to *cardiomegaly and high-output congestive heart failure*. With extensive hemolysis, the fetus becomes *progressively anemic, and large iron stores may be present in the liver and spleen*. When the fetal hematocrit falls much below 15%, severe edema, ascites, and anasarca develop – the condition known as **hydrops fetalis**.

Pathologic Features

The pathologic features of the placenta in erythroblastosis fetalis are not specific. They develop largely because of the fetal anemia and cardiac failure, and therefore the intensity of the findings is related to the severity of those conditions. The presence of **placental hydrops** parallels that of fetal hydrops. Thus, the most striking feature of the placenta in erythroblastosis fetalis is the *pallor and marked uniform enlargement*. The villous tissue is diffusely *pale, boggy, and friable* (Fig. 20.1). Rarely, one observes gross icteric staining of placental surface vessels and umbilical cord.

Microscopically, the most striking feature is *villous enlargements and edema* (Fig. 20.2). *Bone marrow elements and hematopoiesis* are present in the fetal circulation (Fig. 20.3). Fetal NRBCs are particularly prominent. Additional histologic features in the placenta are *villous immaturity* (Fig. 20.4), *a marked decrease in the number of fetal vessels, and an increased number and size of Hofbauer cells* (Fig. 20.5). On occasion, one may find

Figure 20.1. Cut sections of a placenta with hydrops in an infant with erythroblastosis fetalis. Note the extreme pallor of the villous tissue.

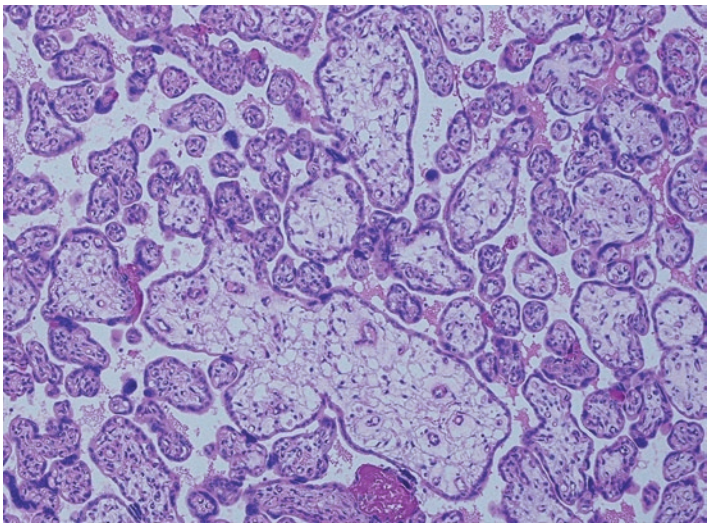

Figure 20.2. Placenta with hydrops demonstrating enlarged villi with edema. H&E ×160.

small amounts of hemosiderin deposited in chorionic *macrophages* betraying the long-standing hemolysis, but this is usually not a prominent finding. *Intervillous thrombi* are also common in erythroblastosis fetalis (see Fig. 19.3 in Chap. 19). It is likely that the villous edema so alters the intervillous blood flow as to cause local eddying and stasis, with thrombosis the end result. Nevertheless, since NRBCs are often found in the thrombi, *fetal bleeding must occur at times* and is likely due to local villous hypoxic injury.

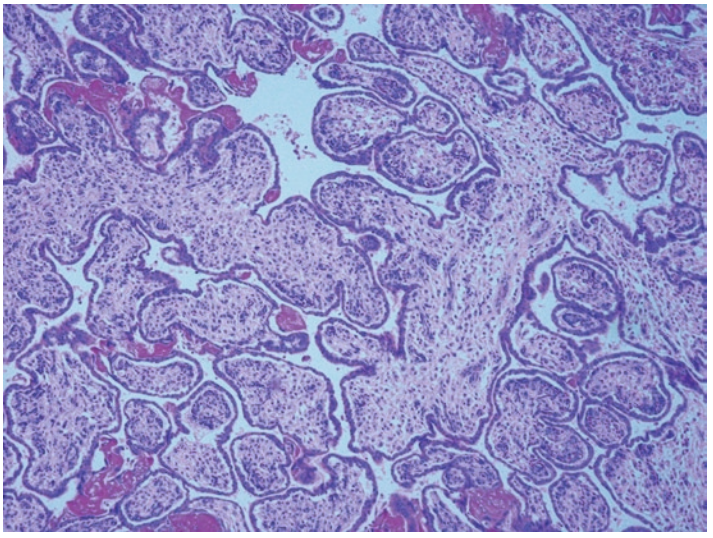

Figure 20.3. Placenta in fetal hydrops. Note the abundant NRBCs in the fetal capillaries. H&E ×640.

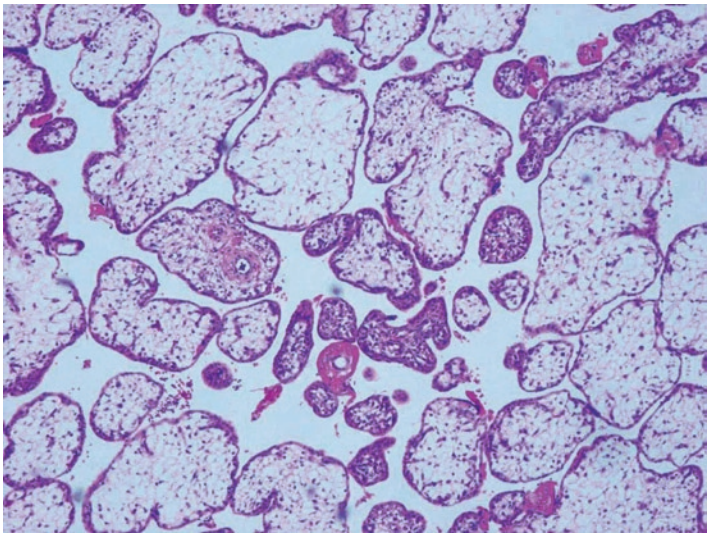

Figure 20.4. Immature appearing, edematous villi in the setting of fetal hydrops. H&E ×100.

Clinical Features and Implications

Fetal hydrops is now readily diagnosed sonographically. If the hydrops is due to hemolysis, it may be quickly reversed through prenatal transfusion (transabdominally or by cordocentesis), thus restoring oxygenation. Although intrauterine transfusions are not without significant risk, the morbidity and mortality of untreated infants is very high. *Hepatosplenomegaly* is prominent, and usually infants have

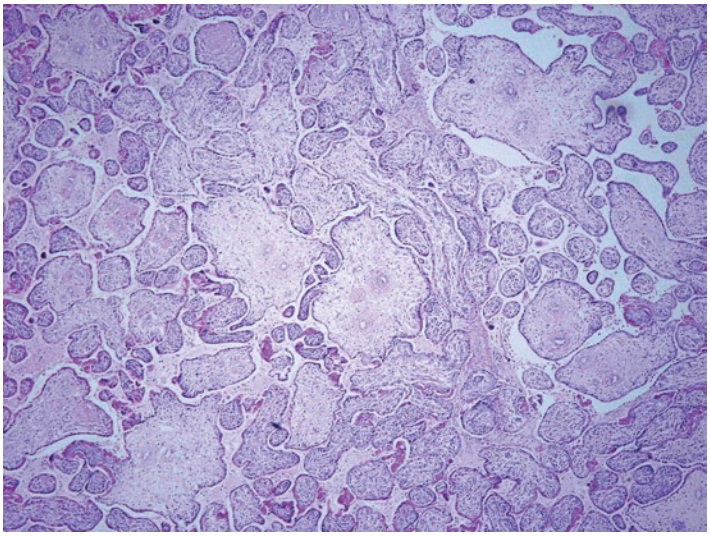

Figure 20.5. Stillborn with typical erythroblastosis fetalis showing edema, abundance of Hofbauer cells and persistent cytotrophoblast. Because of fetal demise, the fetal vessels are obliterated. H&E ×250.

some degree of *hypoproteinemia, thrombocytopenia, and increased beta-cell activity of the islets of Langerhans* (due to insulin binding by the circulating hemoglobin). Elevated serum levels of human chorionic gonadotropin (hCG), human placental lactogen (hPL), and placental protein 5 (PP5) may be present, which are presumably due to the increased placental mass. Occasionally one sees large *maternal ovarian lutein cysts* and *fetal ovarian cysts* due to the elevated hCG.

Hematologic Disorders

Clinical Features and Implications

Normal adult hemoglobin molecules contain two pairs of polypeptide (globin) chains, the **α-chains** and **β-chains**. In embryonic and fetal life, special forms of hemoglobin are prevalent at carefully scheduled times. *Abnormal construction of the globin chains results in altered hemoglobins that may be deficient in oxygen-carrying capacity*. This, in turn, can lead to abnormal red blood cell shapes, as in sickle cell disease. In **α- and β-thalassemias**, *anemia results from a decreased* ***production*** *of normal hemoglobin.*

Homozygous **α-thalassemia** is inherited as an autosomal *recessive*, and therefore has a recurrence rate of 1 in 4. The pathology in the newborn is essentially identical to that of Rh-disease and it is lethal unless intrauterine blood transfusions are performed. The abnormal gene for α-thalassemia (α-thal$_1$) is common in Indonesians, Filipinos, Thais, Chinese, Germans, African-American, and Canadian Asians. It is also common in Kurdish and Ashkenazi Jews, but in those populations it has not been associated with hydrops. The frequency of this deletion of α-chain genes is greatest in Indonesians and Chinese.

Bart's hemoglobin disease occurs when the *α-chains are replaced by gamma chains (γ-chains)*. The γ-chains are often heterogeneous, and different chain compositions cause different severities of the disease. *Hydrops occurs when the γ-chain gene is homozygous and the four α-chains are replaced by four tau chains (τ-chains)*. The defective hemoglobin is unable to release its oxygen effectively, causing tissue hypoxia, fetal cardiac failure, and hydrops. It is lethal at birth or very shortly thereafter. The fetal red blood cells are frequently *misshapen* and may even be *sickled*. *Cardiac hypertrophy* is often striking, as is the extensive, widespread *extramedullary hematopoiesis*.

In **hemoglobin-H disease**, the hemoglobin molecule consists of *four β-chains*. This particular hemoglobinopathy is prevalent in Asians, and although it causes neonatal anemia, hydrops has not been described. The same is true of **sickle cell anemia** and **sickle cell β-thalassemia**. Both are associated with poor reproductive outcome, but do not feature hydrops as a complication.

Hemoglobin electrophoresis is perhaps the simplest and most widely available tool for the differential diagnosis of the various types of hemoglobin. Chorionic villus sampling (CVS) has made possible the accurate diagnosis of sickle cell disease and thalassemia by direct globin gene analysis. *Appropriate samples of blood should be saved for such studies at autopsy when the etiology of hydrops is uncertain*. The aforementioned methods also much facilitate the diagnosis of heterozygotes.

Pathologic Features

The placentas in these disorders do not differ very much from those with classical erythroblastosis. *Histology alone cannot make the correct differential diagnosis*. The placental enlargement may be massive and is usually *even more enlarged than in classic erythroblastosis*. Placentas weighing up to 3,500 g have been described. The placenta is also *pale, friable, and edematous*. Microscopically, the *cytotrophoblast is prominent* and, in the much-enlarged fetal circulation, large numbers of *red-cell precursors* are found. Pigment is occasionally seen within *chorionic macrophages* either representing hemosiderin or bilirubin from bilirubinuria and liver damage. Preeclampsia is a frequent corollary of this condition, presumably because of the massive placental enlargement.

Trauma

Fetal hemorrhage with resultant hydrops may occur due to various traumatic events. An example is **cordocentesis**, which is usually a benign procedure, but rarely hemorrhage has led to exsanguination. If the infant survives and if severe bleeding has occurred, the resultant anemia can lead to hydrops. Thrombosis of umbilical vessels due to cordocentesis has also been described. In addition, it carries a risk of *transplacental hemorrhage* and, thus, the possibility of *maternal alloimmunization*. **Retroplacental hematoma** (abruptio), although usually associated with maternal bleeding, may sometimes be associated with fetal hemorrhage. Blunt abdominal trauma to the mother without

abruption may also be associated with fetal hemorrhage. It is thought that trauma from fetal movement, such as "kicking" the placenta, may cause hemorrhage; however, that has not been proved. Many cases of totally unexplained acute exsanguinations have also occurred.

Miscellaneous Causes of Fetal Hydrops

Occasionally, *tumors or tumor-like lesions may lead to significant fetomaternal hemorrhage, fetal hemorrhage, or hydrops*. For example, placental **choriocarcinomas** (see Chap. 24) may invade villous tissue and cause fetal vascular discontinuity. Discovery of placental choriocarcinomas is usually fortuitous, and perhaps other "unexplained" transplacental hemorrhages would yield similar lesions, if the placenta were examined in more detail. **Chorangiomas** may also be the source of transplacental hemorrhage (see Chap. 22), and hydrops may develop secondary to sequestration of fetal blood cells and due to obstructed venous return from the placenta. **Hemangiomas** of the umbilical cord have also led to hydrops. Other fetal tumors associated with hydrops are listed in Table 20.1.

Fetal hydrops may be associated with various congenital syndromes, in particular, the **Beckwith–Wiedemann syndrome**. *Placentomegaly* is quite common in this disorder, and *hydrops* has been described. The placenta often shows *villi with lacunar, hydropic expansion, and focal chorangiomatosis* (Fig. 20.6). Venous thrombi have been described, as have edematous and excessively *long umbilical cords*. The placental and cord enlargement may be secondary to the dysregulation of normal growth control seen in this syndrome. It is not completely clear what is the etiology of the hydrops in these cases. Hydrops may also be associated with a number of metabolic storage disorders (see below).

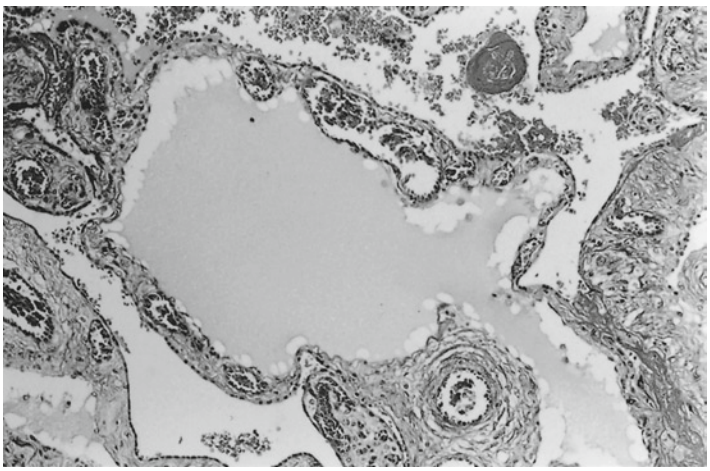

Figure 20.6. Villous alteration in the placenta of a case of Beckwith-Wiedemann syndrome shows a massive cistern, chorangiosis, and congestion. Placentomegaly was also present, and the cord was 69 cm in length with a true knot. Masson trichrome ×160.

Hydrops is associated with various infections (Table 20.2; see Chap. 16). Finally, hydrops may be **idiopathic**. However, as more cases are being investigated, the number of cases that cannot be explained is diminishing. The indications are that, with careful prenatal sonographic surveillance and with the help of more sophisticated autopsy and molecular techniques, this entity may vanish in future. Some of the rarer entities that cause fetal hydrops should be considered before evoking this diagnosis.

Suggestions for Examination and Report
(Fetal or Placental Hydrops)

Gross Examination: A description should be made of the pale, hydropic nature of the placenta. If a fetal demise has occurred, and the etiology is unknown, blood should be submitted for hemoglobin analysis. Furthermore, the presence of a pale placenta or placental hydrops is an indication of fetal anemia even without clinical history. In these cases, and particularly if there has been a fetal demise, it is recommended that the clinicians be contacted to ensure that a Kleihauer–Betke has been done to rule out fetomaternal hemorrhage (see below). It is also prudent to fix a small amount of tissue for electron microscopy in the event the hydrops is due to a metabolic disorder (see below).

Comment: The histologic features are consistent with hydrops. Hydrops has a varied etiology and clinical correlation is necessary for diagnosis.

Fetomaternal Hemorrhage

Pathogenesis
Despite the anatomic separation of the fetal and maternal circulations, transplacental transfer of blood occurs. Transfer of blood from mother to fetus is rare, but the fetus often bleeds into the maternal circulation. The reason for this fetal bleeding is usually obscure. Etiologic factors that have been implicated include *cesarean section delivery, external fetal version, traumatic amniocentesis, maternal trauma, placental abruption, placental tumors (chorangioma, choriocarcinoma), subchorionic hematomas, tight nuchal cord, and tumultuous labor* but most are idiopathic. In the majority of cases, hemorrhage is of a minor degree, but rarely is it a cause of fetal death (approximately 1:2,000 deliveries). The prenatal diagnosis of a **fetomaternal hemorrhage** may be suggested by certain fetal heart tracing abnormalities, such as a sinusoidal rhythm.

Pathologic Features
One should suspect transplacental bleeding when placenta and villous tissue is *unusually pale*. This observation presupposes that the examiner is familiar with the "normal" color of the placental tissue at different stages of gestation. The presence of *intervillous thrombi* may be

another clue signaling that hemorrhage has occurred through the placenta and may even signify the point of origin of hemorrhage. In some cases, large intervillous thrombi or many intervillous thrombi may be present, while in other cases they may be absent. Intervillous thrombi may occur for other reasons. The villous tissue is also unusually *thick as well as pale*, but not so overtly hydropic as in thalassemia or erythroblastosis. A marked increased in the NRBCs in the fetal circulation of the placenta are also an important pathologic finding (Fig. 20.7).

Clinical Features and Implications

Significant **fetomaternal hemorrhage** may cause *severe fetal anemia, hemorrhagic shock, hydrops fetalis, maternal isoimmunization, fetal cardiac arrhythmias, and fetal or neonatal death. Cerebral palsy, cerebral infarcts, and microcephaly* have also resulted, presumably due to acute hypotension. In a massive, chronic fetomaternal hemorrhage, hydrops may result from cardiac failure, and brain injury is common. In an acute, massive fetomaternal hemorrhage, fetal death is often the result. Loss of 20% of blood volume is sufficient to produce signs of shock and loss of greater amounts will result in death.

In the event of an *unexplained stillbirth, marked placental pallor, or significant neonatal anemia, the maternal blood should be examined for fetal cells*. This may be done using the **Kleihauer-Betke test**. This technique depends on the fact that fetal hemoglobin is less soluble than maternal (adult) hemoglobin in an acid milieu. Air-dried maternal blood films are fixed, eluted in buffer, and stained. Fetal red blood cells maintain their color but, because the maternal hemoglobin is largely eluted, the maternal cells appear as mere shadows (Fig. 20.8). Ten fields at 250× magnification are reviewed and fetal and maternal cells are counted. The results are reported as a percentage of fetal red blood cells in the

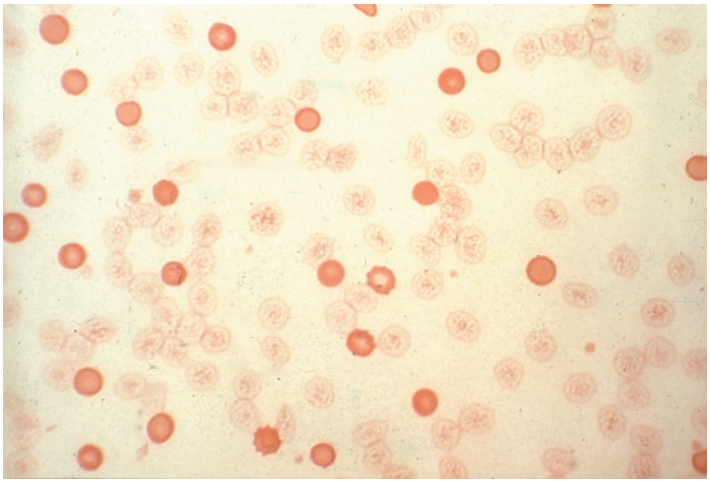

Figure 20.7. Kleihauer-Betke stain of maternal blood. The darkly stained cells are fetal erythrocytes and there are approximately 5% of cells staining. Eosin; Kleihauer. ×1,000.

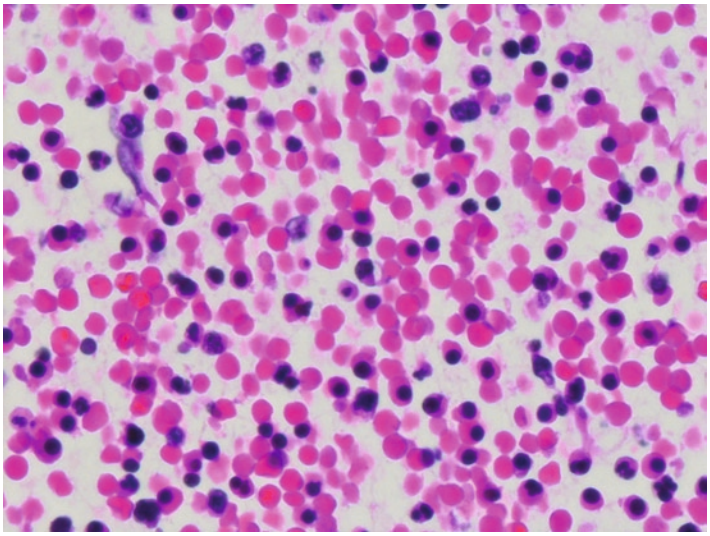

Figure 20.8. Numerous nucleated red blood cells within fetal capillaries. H&E ×200.

maternal circulation and based on a maternal blood volume of approximately 5,000–6,000 mL. One can thus calculate:

$$\_\,\%\ \text{fetal cells} \times 5{,}000\ \text{mL} = \_\,\text{mL of fetal blood in maternal circulation}$$

The blood volume of the infant can be estimated to be approximately 80 mL/kg body weight, with perhaps half again as much present in the placenta. Therefore, the volume of hemorrhage relative to the total fetal blood volume can also be determined. It is important to realize that if a *large quantity of fetal blood* is present in the mother, particularly if it is *equal to or greater than the blood volume of the infant*, a chronic hemorrhage should be suspected.

While the life span of fetal cells in the maternal circulation is somewhat shorter than that of normal cells, transplacental bleeding may be ascertained for as long as *4–6 weeks after delivery* by Kleihauer-Betke tests alone. All the cells will be gone 3 months after delivery. Unfortunately, the test is, at times, inaccurate. Falsely high values may result from maternal sources of hemoglobin F (present in 25% of pregnant women), for instance in β-thalassemia minor. On the other hand, there will be an *underestimation of fetal blood loss* or false-negative results for the following reasons:

- Only 90% of the fetal cells will stain, as 10% already contain hemoglobin A.
- Some fetal cells die, the number being dependent on the time since the hemorrhage.
- ABO incompatibility between mother and fetus clears fetal cells rapidly.
  - For example, if the mother is blood group O and the fetus is A, the fetal cells will be rapidly cleared by maternal anti-A antibody.

Other tests used in the determination of the presence and/or quantification of fetomaternal hemorrhage are **α-fetoprotein** and **flow cytometry**. These tests have also been used after Rh-negative women give birth to an Rh-positive infant to determine the amount of Rhogam prophylaxis necessary.

Suggestions for Examination and Report
(Suspected fetomaternal hemorrhage)

Gross Examination: If the placenta is markedly pale, fetal anemia should be suspected.

Comment: If there is placental hydrops and the presence of numerous NRBCs, a fetomaternal hemorrhage should be suspected and there should be a recommendation for a Kleihauer-Betke test.

Fetal Nucleated Red Blood Cells

It is known that **nucleated red blood cells (NRBCs)** appear in the circulation of *anemic fetuses*, and this is best exemplified in erythroblastosis fetalis (Fig. 20.7). Similarly, there is an increase in NRBCs with *acute blood loss* and in fetuses experiencing *hypoxia*. This feature plays an important role in current medicolegal decisions. One of the most important aspects to the presence of elevated NRBCs in the fetal circulation is how rapid the response is to the loss of red cells and hypoxia, and whether this response is quantitatively reflected in the number of the NRBCs in the circulation.

Studies have shown that NRBCs disappear by the end of the third month of pregnancy. In the histologic evaluation of placentas *only rare NRBCs should be observed in the term placenta*. When NRBCs are present in the fetal blood, and thus in the fetal vessels in the placenta, it is a distinctly abnormal finding. The pathologist should then try to find the reason for their presence. An absolute value *greater than* 1×10^9*/L should be considered as a potential index of intrauterine hypoxia*. Normally there are about 200–600 NRBCs/mm^3 and 10,000–30,000 white blood cells (WBC). However, *infants of diabetic mothers have increased numbers, as do growth-restricted infants*. NRBCs that already formed may be released initially, but because of the complex sequence of signals to initiate erythropoiesis and release of NRBCs, many hours must pass from the initiation of a hypoxic stimulus to the appearance of *significant* numbers of NRBCs in the circulation.

Suggestions and Examples for Report
(Nucleated Red Blood Cells)

Gross Examination: NRBCs are not evident on gross examination.

Comment: The presence of increased NRBCs may be indicative of fetal anemia and if this can be ruled out, is indicative of intrauterine hypoxia.

Transplacental Passage of Cellular Elements

While transplacental red blood cell passage has the most serious consequences due to anemia and immunization, **transplacental white blood cell transfer** is also of interest. Fetal lymphocytes pass to the mother in most normal pregnancies and may be found years postpartum in the maternal blood or bone marrow. Of course **deported syncytiotrophoblast** traveling from the placenta to the maternal lung has long been known. **Transplacental passage of tumor cells** or metastasis from mother to fetus has also been described many times (see Chap. 22). Chimerism, induced by prenatal **maternal lymphocyte transfer**, has also been reported. A few additional reports of 46 XX cells in the circulation of male fetuses have been forthcoming. Such passage is clearly exceptional. There have also been occasional reports of fetal plethora that were apparently due to **mother-to-fetus blood transfer**; however, numerous studies have affirmed the transfer of small numbers of maternal red blood cells to the fetus without fetal plethora or abnormal placentas.

Fetal Metabolic Storage Disorders

Many of the **metabolic storage disorders** produce inclusions or vacuoles in the tissues of affected individuals. In some, involvement of placental tissues enables prenatal diagnosis via chorionic villus biopsy or from material obtained at amniocentesis. Many of these diseases may cause fetal *hydrops*, the etiology of which remains obscure. Nevertheless, because of the association with storage disorders, *cases of nonimmune hydrops fetalis warrant special attention*. Many of the inclusions are highly water and/or lipid-solvent soluble and can only be identified with proper fixation. *Electron microscopy* and *special enzyme studies* are often necessary to make the definitive diagnosis. Therefore, consideration should be given to fixation of tissue for electron microscopy when one of these disorders is suspected. Importantly, there are numerous cases in which a *storage disorder was suspected only after placental examination* revealed characteristic features. Even without clinical suspicion or evidence of disease, the presence of **foam cells**, **trophoblastic vacuolization**, and **irregular calcification** *is indicative of an unidentified fetal storage disorder*. Further workup is then warranted.

Pathologic Features

Macroscopically, the placenta will be *enlarged, pale, and/or soft*, particularly in cases associated with hydrops. On microscopic examination, intracellular accumulation of material is revealed as *vacuolization of the cytoplasm* of certain cells, the distribution of which is particular to that storage disorder. Because the cellular glycolipids are highly water-soluble, the empty appearance of the vacuoles is the usual finding in many fetal storage disorders. In the majority of the disorders with placental manifestations, it is primarily the *syncytiotrophoblast* that shows the typical vacuolated cytoplasm (Fig. 20.9). Other trophoblastic cells may show vacuolation as well, including *cytotrophoblast and extravil-*

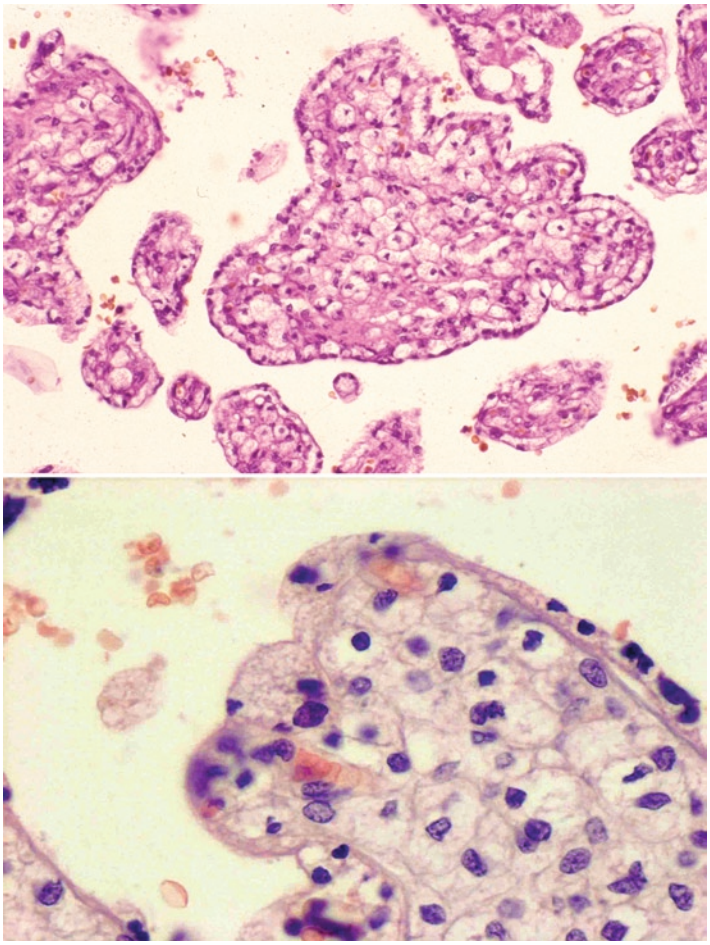

Figure 20.9. (**a**) Chorionic villi affected by Hurler's Disease (mucopolysaccharidioses I) with vacuolization of syncytiotrophoblast as well as Hofbauer and stromal cells. H&E ×240. (**b**) Villus affected by mucolipidosis II (I-cell disease). Note the abundance of vacuoles in the syncytium and Hofbauer cells. H&E ×360.

lous trophoblast. Furthermore, *villous fibroblasts, Hofbauer cells, villous capillary endothelial cells, and, rarely, the amnion* may show vacuolization. Endothelial damage, perhaps secondary to lipid accumulation, is seen in a number of storage diseases leading to *thrombosis* of chorionic or fetal stem vessels.

If vacuolization of cells in the placenta is identified, a metabolic storage disorder may be tentatively diagnosed. Based on which cells contain the vacuolization, whether the infant or fetus has hydrops and other clinical information, a differential diagnosis may be compiled. Table 20.2 lists selected storage disorders and the particular placental cells in which vacuolization can be identified. Histochemical stains can be helpful in differentiating some of these disorders, but this has not been studied on placental tissue in every disorder. After making the tentative diag-

nosis of storage disorder, diagnosis and confirmation of the specific disease must be made via enzyme or other special studies.

Specific Disorders

A few specific disorders are mentioned here, as they show some unique features. For instance, **Morquio disease** or **mucopolysaccharidosis type IV**, unlike many of the storage diseases, only rarely has histologic evidence of storage products in trophoblast, but rather shows *granularity in Hofbauer cells*. The absence of β-galactosidase defines **type 1 G_{M1} gangliosidosis**. Typical inclusions or *zebra bodies* may be ultrastructurally identified in the fetal ganglion cells. Fetal cells will be unremarkable in paraffin sections, but *"empty vacuoles" in the syncytial cytoplasm, the amnionic epithelial cells, and Hofbauer cells* are present. Occasionally, vacuolization has been demonstrable in endothelial cells in villous stem vessels, and *calcified thrombi* in large fetal vessels have also been identified. Since membrane-bound inclusions are present in amnionic cells, diagnosis can be made from cells cultured from the amniotic fluid. **Tay–Sachs' disease (G_{M2}-gangliosidosis type I)** produces *vacuolization of syncytiotrophoblast*. In **G_{M2}-gangliosidosis type II**, **Sandhoff's disease**, vacuolation is seen in *stromal* as well as the *syncytial* cells. Ultrastructurally, the most striking feature is the occurrence of *parallel membranous arrays in occasional lysosomes* in stromal cells.

Niemann–Pick disease Type A, which is due to sphingomyelin diphosphodiesterase deficiency, can be diagnosed from the absence of the enzyme in amniotic fluid. Unusual *echogenic densities in the placentas* of several cases have been demonstrated sonographically and these placentas have had *thick chorionic plates*. *Vacuolated syncytium, Hofbauer cells,* and *fibrocytes* contain accumulations of sphingomyelin, which is also present in the umbilical cord and the chorion laeve.

Gaucher's disease is a heterogeneous disease that may cause *fetal hydrops*. The placenta is *large* and *edematous* with macroscopic features similar to that of erythroblastosis fetalis. In the absence of hydrops, there are generally no placental findings. However, some cases may show *Hofbauer cells with minimal vacuolization*. Uncommonly, characteristic histiocytes, or *Gaucher cells*, may be found in fetal vessels in the placenta. Absence of α-galactosidase A results in **Fabry's disease**, a disorder of glycosphingolipid metabolism. The tissues accumulate ceramide trihexose. Although the syncytiotrophoblast does not show vacuolization, the *decidual cells* and *decidual vessels* contain *argyrophilic granules*, which, by electron microscopy, have the appearance similar to zebra bodies. The fetal portions of the placenta are normal.

Mucolipidosis type II or **I-cell disease** is a rare and fatal disorder whose genetic transmission is autosomal recessive. *Periodic acid-Schiff (PAS)-positive lysosomal inclusions* are present in the cells of affected children, including kidney cells, leukocytes, and fibroblasts. The typical "inclusions" cannot be seen in paraffin-embedded sections, but are obvious in epoxy-embedded material. Placental involvement with inclusion-bearing cells in the *villous fibroblast* has also been demonstrated. In paraffin sections of the placenta, the *vacuoles of formerly mucolipid-containing lysosomes* are readily apparent in the *syncytium* and in *Hofbauer cells* (Fig. 20.9). The features are much enhanced by process-

ing the tissues in epoxy resin. In some cases vascular lesions have been present in the *villous stem arteries ranging from fibrinoid necrosis to complete obliteration*. Focal *villous calcification* is also a common finding. As with many of these disorders, diagnosis may be made with electron microscopy.

Unusual placental findings in **Pompe's disease** or **glycogen storage disease type II** consist of *cytoplasmic vacuolation of syncytium, cytotrophoblast, fibroblast, and amnionic connective tissue cells*. By electron microscopy, typical *membrane-bounded, glycogen-filled inclusions in capillary endothelial cells and villous fibroblasts* are found. These inclusions may be found in cells obtained via CVS as early as 10 weeks. In **type IV glycogen storage disease**, vacuoles are only present in the *amnionic epithelium*.

Suggestions for Examination and Report
(Storage disorders with vacuolization of trophoblast or other cells)

Gross Examination: Generally, the placentas in these disorders are grossly unremarkable, but may be pale, enlarged and soft, particularly if hydrops is present. If a disorder is suspected, tissue should be fixed for electron microscopy.

Comment: Vacuolization of trophoblast or other placental cells is highly suggestive of a fetal metabolic disorder and further testing should be suggested.

Placental Changes in Intrauterine Fetal Demise

After death in utero, the fetal tissue begins to undergo autolysis. Certain placental changes also occur that are attributable to fetal death, which are different from the pathologic changes that are the cause of death. Macroscopically, the *fetal surface and fetal membranes may be discolored red-brown* due to hemolysis. Microscopically, the pathologic changes in the placenta that are directly caused by the fetal demise mostly relate to the *cessation of fetal circulation*. This causes *progressive sclerosis of the fetal vessels* and ultimately their *obliteration*. This is particularly true of the villous capillaries and thus leads to widespread *avascular villi*. Studies have shown that these and other changes occur after fetal death in a relatively predictable manner such that the time of fetal death may be roughly estimated by the presence of absence of particular features.

One of the first changes that occur is **intravascular karyorrhexis** in villous capillaries. This consists of particles of nuclear debris, predominantly derived from leukocytes, stained deeply with hematoxylin, present within villous capillaries and small villous vessels (Fig. 20.10). This change is not present if fetal death has occurred less than 6 h prior to delivery. Another early change is **degeneration of the umbilical vascular smooth muscle cells**. This finding may be present within a few hours but is present in virtually all cases by 12 h. It consists of some *loss of nuclear basophilia* and *nuclear pyknosis*. In addition, the *smooth muscle cells become thin and spindled*, also taking on a *"wavy"*

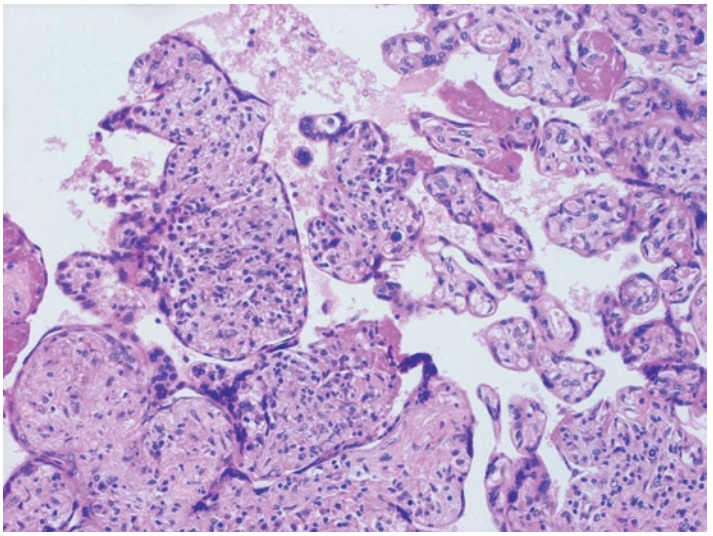

Figure 20.10 Intravascular karyorrhexis with nuclear debris in fetal capillaries. H&E ×140.

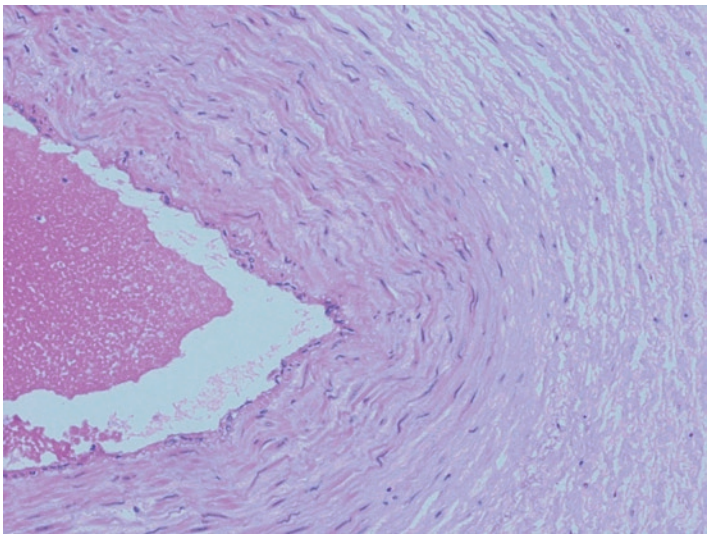

Figure 20.11. Degeneration of vascular smooth muscle of umbilical cord after demise. H&E ×200.

appearance (Fig. 20.11). The loss of fetal circulation also causes **luminal abnormalities of the fetal stem vessels** consisting of *septation of the lumen and obliteration* (Fig. 20.12). The septation commonly appears as the presence of *multiple irregular lumens connected by thin fibrous tissue* containing degenerated blood and occasionally thrombi. If these changes are multifocal and present in 10–25% of stem villi, then the time from fetal death is at least 48 h. The changes do not become exten-

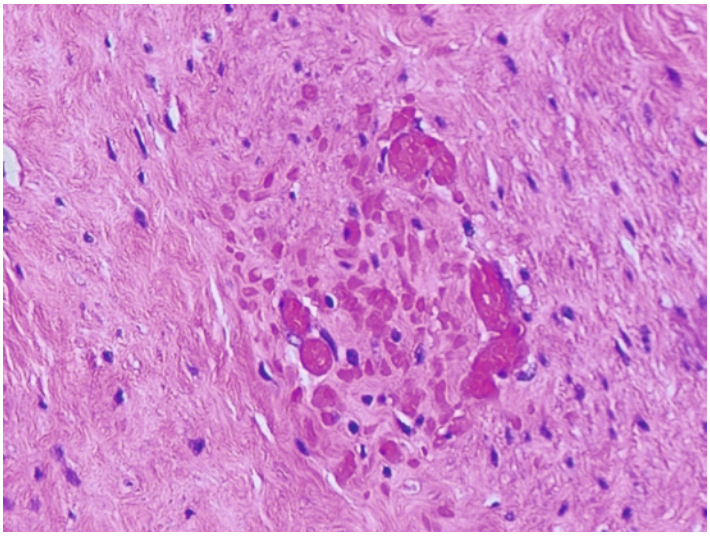

Figure 20.12. Stem vessel luminal abnormalities, septation, and fibromuscular sclerosis with partial obliteration. H&E ×400.

sive, involving more than 25% of the stem villi, until approximately 2 weeks after fetal death. *Sclerosis of the villous stroma or avascular villi* often accompanies obliteration of the fetal vessels. Extensive avascular villi, involving at least 25% of the terminal villi, also occur roughly 2 weeks after fetal demise. The luminal abnormalities described above can also be seen in live-born fetuses when there is cessation of fetal blood flow secondary to fetal vascular thrombosis (see Chap. 21). Therefore, in stillborn fetuses caution should be used in attributed these changes to thrombosis, as they can be due solely to fetal death. Correlation with autopsy findings and known time of death may be helpful in these cases.

Other changes also occur but in a less predictable manner. Some authors have suggested that **increased syncytial knots** are associated with fetal death, while others do not find this association. It is our experience that this change may occur, but when it does it is usually in cases with long-term intrauterine retention of the placenta after fetal death, on the order of weeks to months. It is, however, important to note that although there is some decrease in maternal blood flow after fetal death, flow does not completely stop nor does it impair the viability of the trophoblast. Thus, weeks and even months after fetal death when the villous stroma is completely avascular and hyalinized, the trophoblastic cover can continue to be viable. After fetal death, **villous stromal microcalcification** may be present consisting of fine, *granular calcification of the trophoblastic basement membrane* or fine, punctate granules within the stroma (Fig. 20.13). It is likely that calcium is not the sole mineral that deposits within the villi in this situation. Normally, the fetal vessels transport these minerals away from the placenta,

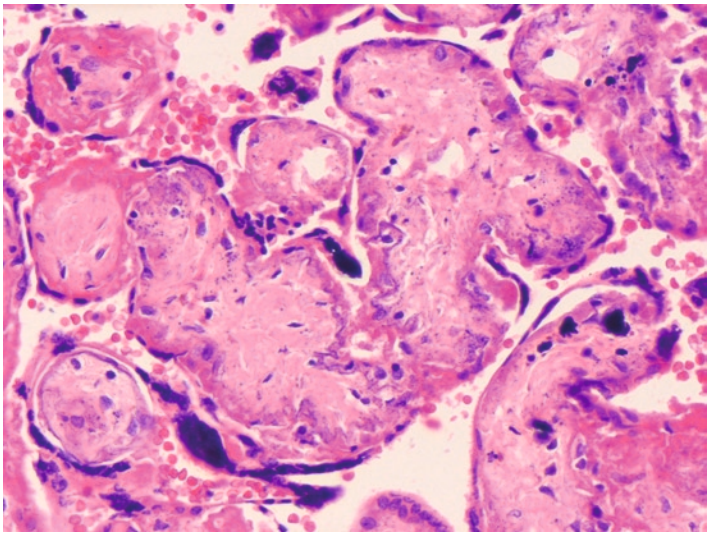

Figure 20.13. Microcalcification of trophoblastic basement membrane. H&E ×200.

but with the loss of fetal circulation, there is accumulation and deposition within the villous stroma and the trophoblastic basement membrane. Other changes that may occur with fetal death include **thickening of the trophoblastic basement membrane** and **degeneration of Wharton's jelly**.

Suggestions for Examination and Report
(Fetal demise)

Gross Examination: The cord and fetal surface may be hemolyzed and discolored red. No additional gross examination or sections need to be submitted if the cause of demise is known. If it is not, 4–5 additional random sections of villous tissue should be submitted to identify possible causes of demise.

Comment: The changes seen should be described and it should be indicated that they are consistent with fetal demise. The approximate timing of fetal death can be included. Certainly a comment on possible placental causes of death should be made based on pathology found on examination.

Table 20.1. Causes of nonimmune hydrops fetalis.

Cardiovascular: congenital heart disease
Coarctation of the aorta
Hypoplastic left heart
Cardiac arrhythmias particularly supraventricular tachycardia
Premature closure of the foramen ovale
Endocardial fibroelastosis
Ebstein's anomaly of the tricuspid valve
Chromosomal (see Chap. 11)
Turner's syndrome, 45 XO
Trisomy 13, 15, 16, 18, and 21
Duplications of the long arms of chromosomes 15 or 17
Triploidy
Anemia
Twin to twin transfusion syndrome (see Chap. 10)
Thalassemia
Fetomaternal hemorrhage
Hemolytic anemia
Fetal hemorrhage
Disrupted velamentous or other fetal vessels (see Chap. 15)
Injury to the fetus
Thoracic: space-occupying lesions
Cystic adenomatoid malformation and pulmonary sequestration
Diaphragmatic hernia
Cystic hygroma
Chylothorax
Lymphangiectasias
Infection (see Chap. 16)
Parvovirus
Cytomegalovirus
Toxoplasmosis
Herpes simplex virus
Syphilis
Rubella
Congenital tumors (see Chap. 22)
Congenital neuroblastoma
Hepatoblastoma
Sacrococcygeal teratoma
Leukemia
Mesoblastic nephroma
Hemangioma
Chorangioma
Choriocarcinoma

Table 20.1. (continued)

Miscellaneous
Malformations of the genitourinary tract
Fetal storage disorders
Thyrotoxicosis
Small bowel volvulus
Intussusception
Trauma
Beckwith-Wiedemann syndrome
Chorangiomatosis
Idiopathic

Table 20.2. Summary of placental findings in metabolic storage diseases.

			Intracellular vacuolization						Histochemistry			
Disorder	**Deficiency**	**Hydrops**	**ST**	**ET**	**HC**	**FB**	**EN**	**AE**	**PAS**	**Alcian blue**	**Colloidal Fe**	**ORO**
Mucopolysaccharidoses									+/−		+	
MPS I (Hurler disease)	α-1-Iduronidase	+	+		+	+						
MPS III (San Filippo disease)	Various		+									
MPS IV (Morquio disease)	Various	+			[a]							
MPS VII (Sly disease)	β-Glucuronidase	+			+							
Sphingolipidoses												
GM1 gangliosidosis	β-Galactosidase		+	+	+	+		+	+	+	+	+
GM2 gangliosidosis												
Type I (Tay–Sachs disease)	β-Hexosaminidase, α subunit		+		+			+				
Type II (Sandhoff disease)	β-Hexosaminidase, β subunit		+			+						
Niemann–Pick disease, type A	Sphingomyelinase	+	+	+	+	+			+/−			+
Niemann–Pick disease, type B	Sphingomyelinase											
Gaucher's disease	β-Glucosidase	+			M				+			
Fabry disease	α-Galactosidase								+			+

Table 20.2. (continued)

			Intracellular vacuolization						Histochemistry			
Disorder	**Deficiency**	**Hydrops**	**ST**	**ET**	**HC**	**FB**	**EN**	**AE**	**PAS**	**Alcian blue**	**Colloidal Fe**	**ORO**
Other lipidoses												
Wolman disease	Acid lipase	+	+									+
Cholesterol ester storage disease	Acid lipase	+	+			+						
Niemann–Pick disease, type C	Unknown											
Neuronal ceroid lipofuscinosis	Unknown		+				+	+				
Mucolipidoses												
Type I, sialidosis	Sialidase		+		+	+						
Type II, I-cell disease	*N*-acetylglucosamine-1-phosphotransferase	+	+	+	+			M	+/−	+/−	+/−	+/−
Type IV	Unknown					+						
Oligosaccharidoses												
Galactosialidosis	β-Galactosialidase	+	+			+						
Sialic acid storage disease (Salla disease)	Sialic acid transporter	+	+	+	+		+	+		+	+	
Glycogen storage disease												
Type II, Pompe disease	α-1,4-Glucosidase		+			+	+		+/−			
Type IV	Amylopectinase							+				

ST syncytiotrophoblast, *ET* extravillous trophoblast or X-cell, *FB* villous stromal fibroblast, *HC* Hofbauer cell, *EN* endothelium, *AE* amnionic epithelium, *PAS* periodic acid-Schiff, *ORO* oil red O, *M* minimal vacuolization[a]Granularity and *not* vacuolization can be seen in Hofbauer cells

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