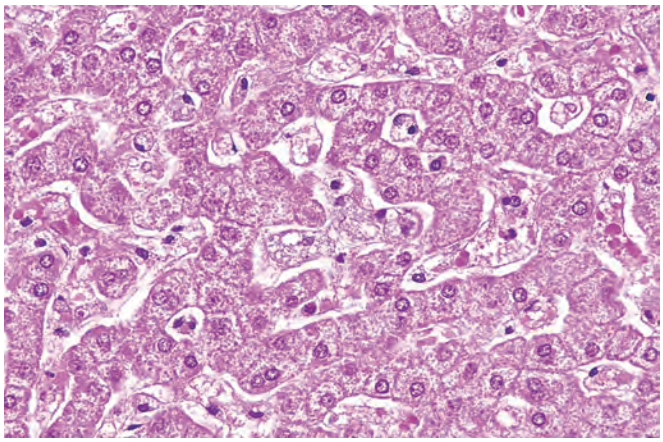

Figure 5-12 Niemann-Pick disease in liver. The hepatocytes and Kupffer cells have a foamy, vacuolated appearance due to deposition of lipids. (Courtesy of Dr. Arthur Weinberg, Department of Pathology, University of Texas Southwestern Medical Center, Dallas, TX.)

Clinical manifestations in type A disease may be present at birth and almost invariably become evident by age 6 months. Infants typically have a protuberant abdomen because of the hepatosplenomegaly. Once the manifestations appear, they are followed by progressive failure to thrive, vomiting, fever, and generalized lymphadenopathy as well as progressive deterioration of psychomotor function. Death comes, usually within the first or second year of life.

The diagnosis is established by biochemical assays for sphingomyelinase activity in liver or bone marrow biopsy. Individuals affected with types A and B as well as carriers can be detected by DNA analysis.

Niemann-Pick Disease Type C

Although previously considered to be related to types A and B, Niemann-Pick disease type C (NPC) is distinct at the biochemical and genetic levels and is more common than types A and B combined. Mutations in two related genes, *NPC1* and *NPC2*, can give rise to NPC, with *NPC1* being responsible for 95% of cases. Unlike most other storage diseases, NPC is due to a primary defect in nonenzymatic lipid transport. NPC1 is membrane bound whereas NPC2 is soluble. Both are involved in the transport of free cholesterol from the lysosomes to the cytoplasm. NPC is clinically heterogeneous. It may present as hydrops fetalis and stillbirth, as neonatal hepatitis, or, most commonly, as a chronic form characterized by progressive neurologic damage. The latter presents in childhood and is marked by ataxia, vertical supranuclear gaze palsy, dystonia, dysarthria, and psychomotor regression.

Gaucher Disease

Gaucher disease refers to a cluster of autosomal recessive disorders resulting from mutations in the gene encoding glucocerebrosidase. It is the most common lysosomal storage disorder. The affected gene encodes glucocerebrosidase, an enzyme that normally cleaves the glucose residue from ceramide. As a result of the enzyme defect, glucocerebroside accumulates principally in phagocytes but in some subtypes also in the central nervous system. Glucocerebrosides are continually formed from the catabolism of glycolipids derived mainly from the cell membranes of senescent leukocytes and red cells. It is clear now that the pathologic changes in Gaucher disease are caused not just by the burden of storage material but also by activation of macrophages and the consequent secretion of cytokines such as IL-1, IL-6, and tumor necrosis factor (TNF).

Three clinical subtypes of Gaucher disease have been distinguished.

- The most common, accounting for 99% of cases, is called type I, or the chronic nonneuronopathic form. In this type, storage of glucocerebrosides is limited to the mononuclear phagocytes throughout the body without involving the brain. Splenic and skeletal involvements dominate this pattern of the disease. It is found principally in Jews of European stock. Individuals with this disorder have reduced but detectable levels of glucocerebrosidase activity. Longevity is shortened but not markedly.
- Type II, or acute neuronopathic Gaucher disease, is the infantile acute cerebral pattern. This form has no predilection for Jews. In these patients there is virtually no detectable glucocerebrosidase activity in the tissues. Hepatosplenomegaly is also seen in this form of Gaucher disease, but the clinical picture is dominated by progressive central nervous system involvement, leading to death at an early age.
- A third pattern, type III, is intermediate between types I and II. These patients have the systemic involvement characteristic of type I but have progressive central nervous system disease that usually begins in adolescence or early adulthood.

MORPHOLOGY

Glucocerebrosides accumulate in massive amounts within phagocytic cells throughout the body in all forms of Gaucher disease. The **distended phagocytic cells, known as Gaucher cells, are found in the spleen, liver, bone marrow, lymph nodes, tonsils, thymus, and Peyer patches.** Similar cells may be found in both the alveolar septa and the air spaces in the lung. In contrast to other lipid storage diseases, Gaucher cells rarely appear vacuolated but instead have a fibrillary type of cytoplasm likened to crumpled tissue paper (Fig. 5-13). Gaucher cells are often enlarged, sometimes up to 100 μm in diameter, and have one or more dark, eccentrically placed nuclei. Periodic acid–Schiff staining is usually intensely positive. With the electron microscope **the fibrillary cytoplasm can be resolved as elongated, distended lysosomes,** containing the stored lipid in stacks of bilayers.

In type I disease, the **spleen is enlarged, sometimes up to 10 kg.** The lymphadenopathy is mild to moderate and is body-wide. The accumulation of Gaucher cells in the bone marrow occurs in 70% to 100% of cases of type I Gaucher disease. It produces areas of **bone erosion** that are sometimes small but in other cases sufficiently large to give rise to pathologic fractures. Bone destruction occurs due to the secretion of cytokines by activated macrophages. In patients with cerebral involvement, Gaucher cells are seen in the Virchow-Robin spaces, and arterioles are surrounded by swollen adventitial cells. There is no storage of lipids in the neurons, yet