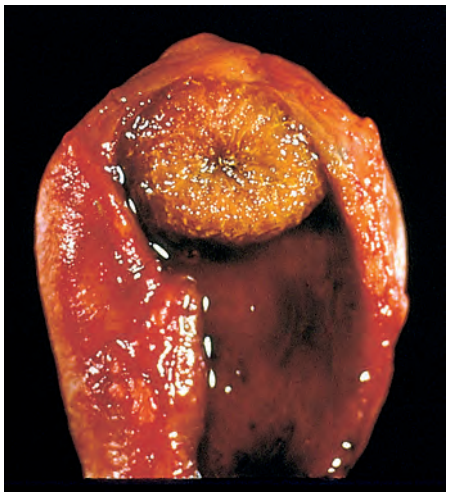

Figure 18-61 Phrygian cap of the gallbladder; the fundus is folded inward.

persons in the United States have gallstones, totaling some 25 to 50 tons in weight. The vast majority of gallstones (>80%) are "silent," and most individuals remain free of biliary pain or other complications for decades. There are two general classes of gallstones: *cholesterol stones*, containing more than 50% of crystalline cholesterol monohydrate, and *pigment stones* composed predominantly of bilirubin calcium salts.

Prevalence and Risk Factors. Certain populations are far more prone than others to develop gallstones. Cholesterol gallstones are more prevalent in the United States and Western Europe (90%) and uncommon in developing countries. The prevalence rates of cholesterol gallstones approach 75% in Native Americans of the Pima, Hopi,and Navajo groups; pigment stones are rare in these populations. Pigment gallstones, the predominant type of gallstone in non-Western populations, arise primarily in the setting of bacterial infections of the biliary tree and parasitic infestations.

The major risk factors associated with the development of gallstones are listed in Table 18-13 and are briefly described here:

- *Age and sex.* The prevalence of cholesterol gallstones increases throughout life but they predominantly affect individuals of middle to older age. Prevalence is higher in females in any region or ethnicity; in Caucasian women it is about twice as high as in men. Hypersecretion of biliary cholesterol seems to play the major role in both age and gender differences. Significant associations are also seen with the metabolic syndrome and obesity.
- *Environmental factors.* Estrogen exposure, including through oral contraceptive use and during pregnancy, increases the expression of hepatic lipoprotein receptors and stimulates hepatic HMG-CoA reductase activity, enhancing both cholesterol uptake and biosynthesis, respectively. The net result is excess biliary secretion of cholesterol. Obesity and rapid weight loss also are strongly associated with increased biliary cholesterol secretion.
- *Acquired disorders.* Gallbladder stasis, either neurogenic or hormonal, fosters a local environment that is favorable for both cholesterol and pigment gallstone formation.
- *Hereditary factors.* Genes encoding hepatocyte proteins that transport biliary lipids, known as ATP-binding cassette (ABC) transporters have associations with gallstone formation. In particular, a common variant of the sterol transporter encoded by the *ABCG8* gene is associated with an increased risk for the development of cholesterol gallstones.

Pathogenesis of Cholesterol Stones. Cholesterol is rendered soluble in bile by aggregation with water-soluble bile salts and water-insoluble lecithins, both of which act as detergents. *When cholesterol concentrations exceed the solubilizing capacity of bile (supersaturation), cholesterol can no longer remain dispersed and nucleates into solid cholesterol monohydrate crystals.* Four conditions appear to contribute to formation of cholesterol gallstones (1) supersaturation of bile with cholesterol; (2) hypomotility of the gallbladder; (3) accelerated cholesterol crystal nucleation; (4) and hypersecretion of mucus in the gallbladder, which traps the nucleated crystals, leading to accretion of more cholesterol and the appearance of macroscopic stones.

Pathogenesis of Pigment Stones. Pigment gallstones are complex mixtures of insoluble calcium salts of unconjugated bilirubin along with inorganic calcium salts. Disorders that are associated with elevated levels of unconjugated bilirubin in bile, such as chronic hemolytic anemias, severe ileal dysfunction or bypass, and bacterial contamination of the biliary tree, increase the risk of developing pigment stones. Unconjugated bilirubin is normally a minor component of bile, but it increases when infection of the biliary tract leads to release of microbial β-glucuronidases, which hydrolyze bilirubin glucuronides. Thus, infection of the biliary tract with *Escherichia coli*, *Ascaris lumbricoides*, or the liver fluke *C. sinensis*, increases the likelihood of pigment stone formation. In hemolytic anemias the secretion of conjugated bilirubin into the bile increases. About 1% of bilirubin glucuronides are deconjugated in the biliary tree, and in the setting of chronically increased secretion of conjugated bilirubin, there is

Table 18-13 Risk Factors for Gallstones

Cholesterol Stones
Demography: northern Europeans, North and South Americans, Native Americans, Mexican Americans
Advancing age
Female sex hormones
Female gender
Oral contraceptives
Pregnancy
Obesity and metabolic syndrome
Rapid weight reduction
Gallbladder stasis
Inborn disorders of bile acid metabolism
Hyperlipidemia syndromes
Pigment Stones
Demography: Asians more than Westerners, rural more than urban
Chronic hemolytic syndromes
Biliary infection
Gastrointestinal disorders: ileal disease (e.g., Crohn disease), ileal resection or bypass, cystic fibrosis with pancreatic insufficiency