hypertension develops over months to years, and its effects are more complex and widespread (see later).

- *Hepatorenal syndrome* is a form of renal failure occurring in individuals with liver failure in whom there are no intrinsic morphologic or functional causes for kidney dysfunction. Sodium retention, impaired free-water excretion, and decreased renal perfusion and glomerular filtration rate are the main renal functional abnormalities. There is decreased renal perfusion pressure due to systemic vasodilation, activation of the renal sympathetic nervous system with vasoconstriction of the afferent renal arterioles, and increased activation of the renin/angiotensin axis, causing vasoconstrition that further decreases glomerular filtration. The syndrome's onset begins with a drop in urine output and rising blood urea nitrogen and creatinine levels.

Chronic Liver Failure and Cirrhosis

The leading causes of chronic liver failure worldwide include chronic hepatitis B, chronic hepatitis C, non-alcoholic fatty liver disease, and alcoholic liver disease. In the United States, chronic liver disease is the twelfth most common cause of mortality, accounting for most liver-related deaths. **Liver failure in chronic liver disease is most often associated with cirrhosis, a condition marked by the diffuse transformation of the entire liver into regenerative parenchymal nodules surrounded by fibrous bands and variable degrees of vascular (often portosystemic) shunting.**

However, not all cirrhosis leads inexorably to chronic liver failure and not all end-stage chronic liver disease is cirrhotic. For example, chronic diseases such as primary biliary cirrhosis, primary sclerosing cholangitis, nodular regenerative hyperplasia, chronic schistosomiasis, and fibropolycystic liver disease are often not accompanied by fully established cirrhosis, even at end stage. On the other hand, patients with well-treated autoimmune hepatitis or those with suppressed hepatitis B or cured hepatitis C often do not progress to end stage, even though they are cirrhotic. *The Child-Pugh classification of cirrhosis* distinguishes between class A (well compensated), B (partially decompensated), and C (decompensated), which correlate with different morphologic features histologically. The utility of such a system is that it helps monitor the decline of patients on the path to chronic liver failure.

Even in diseases that are likely to give rise to cirrhosis, such as untreated viral hepatitis, alcoholic liver disease, non-alcoholic fatty liver disease, metabolic diseases—the morphology and pathophysiology of cirrhosis may be different. Thus, while the term cirrhosis implies the presence of severe chronic disease, it is not a specific diagnosis and it lacks clear prognostic implications. The term *cryptogenic cirrhosis* is sometimes used to describe cirrhosis when there is no clear cause.

MORPHOLOGY

As described, **cirrhosis occurs diffusely throughout the liver, which is comprised of regenerating parenchymal nodules surrounded by dense bands of scar and variable degrees of vascular shunting** (Fig. 18-7). The size of the nodules, the pattern of scarring (linking portal tracts to each other vs. linking portal tracts to central veins), the degree of parenchymal collapse in which no viable liver tissue is present, the range of macroscopic vascular thrombosis (particularly of the portal vein) all vary between diseases and even, in some cases, between individuals with the same disease. Again, to re-emphasize, there is no single cirrhosis, but many cirrhoses. The important details distinguishing cirrhosis of different causes as they pertain to each disease are described in subsequent disease specific sections.

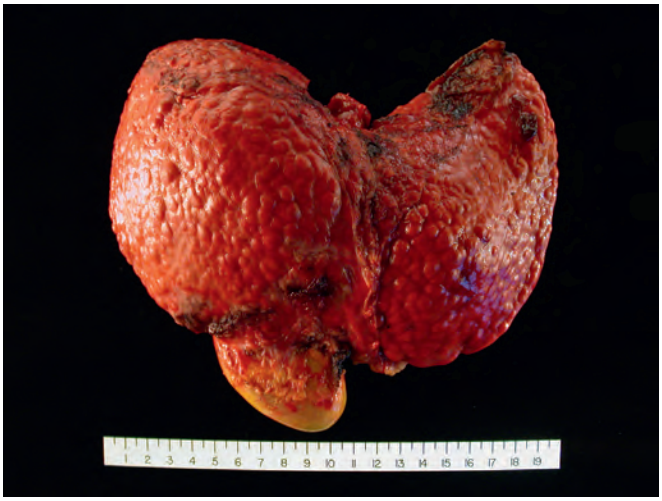

Figure 18-7 Cirrhosis resulting from chronic viral hepatitis. Note the depressed areas of dense scar separating bulging regenerative nodules over the liver surface.

It is becoming increasingly clear that changes identifiable on biopsy in different cirrhotic patients correlate with the prognostically useful Child-Pugh classification mentioned earlier and with portal venous wedge pressures—a new, important, albeit not yet universal method for assessing the presence and degree of portal hypertension. Biopsy specimens demonstrating narrow, densely compacted fibrous septa separated by large islands of intact hepatic parenchyma are likely to have less portal hypertension. Those with broad bands of dense scar, often with dilated lymphatic spaces, with less intervening parenchyma are likely to be progressing toward portal hypertension and, therefore, to end-stage disease.

Clinical implications of these histologic findings and the clinical implications of increased hepatic venous wedge pressures are in the process of being defined. They are expected to play an increasingly important roles in coming years, particularly in patients with chronic hepatitis B and C infections, for whom distinguishing the ebb and flow of cirrhotic features may be essential for determining prognosis as anti-viral treatments improve.

As mentioned earlier stem cell activation is seen in the form of ductular reactions. **In chronic liver disease ductular reactions increase with advancing stage of disease and are usually most prominent in cirrhosis.** There are two correlates of ductular reactions:

- The role of liver stem cells in parenchymal regeneration increases as the preexisting hepatocytes undergo replicative senescence after years to decades of high turnover.
- Ductular reactions may incite some of the scarring in chronic liver disease and thus may have a negative effect on progressive liver disease.