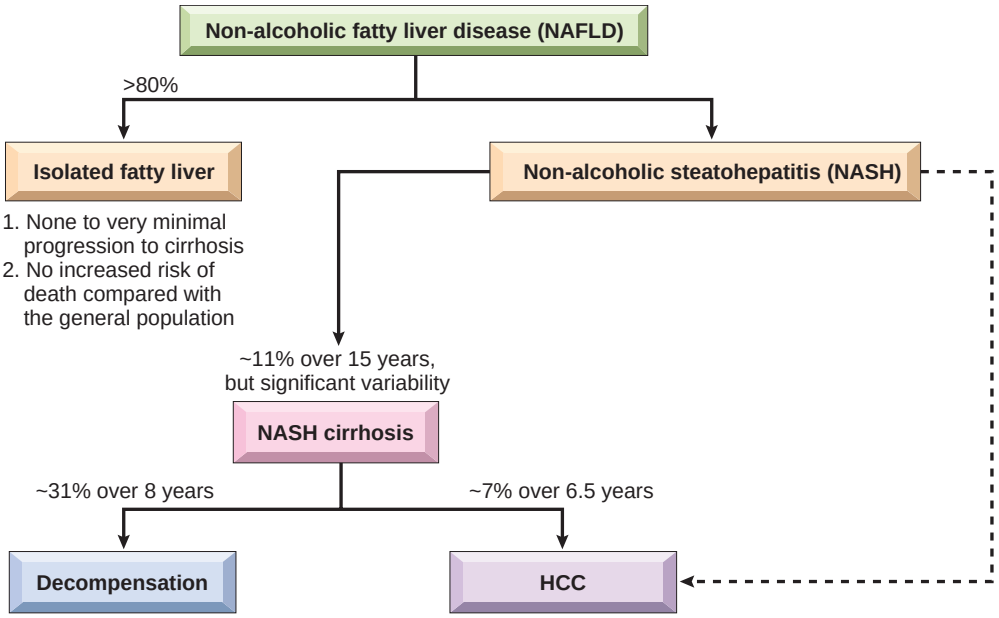

Figure 18-23 Natural history of NAFLD phenotypes. Isolated fatty liver, shows minimal risk for progression to cirrhosis or increased mortality, while non-alcoholic steatohepatitis shows increased overall mortality as well as increased risk for cirrhosis and hepatocellular carcinoma (HCC). DM, Diabetes mellitus.

- Pediatric NAFLD is being increasingly recognized as the obesity epidemic spreads to pediatric age groups, although its histologic features differ somewhat from that seen in adults.

Hemochromatosis

Hemochromatosis is caused by excessive iron absorption, most of which is deposited in parenchymal organs such as the liver and pancreas, followed by heart, joints, and endocrine organs. When hemochromatosis results from an inherited disorder, it is referred to as *hereditary hemochromatosis,* of which there are many forms, some more likely than others to lead to overwhelming iron overload. When accumulation occurs as a consequence of parenteral administration of iron, usually in the form of transfusions, or other causes (Table 18-7), it is called as *secondary hemochromatosis.*

As discussed in Chapter 14, the total body iron pool ranges from 2 to 6 gm in normal adults; about 0.5 gm is stored in the liver, 98% of which is in hepatocytes. In the most severe forms of hemochromatosis, total iron accumulation may exceed 50 gm, more than one third of which accumulates in the liver. The following features characterize severe iron overload in the body:

- Fully developed cases exhibit (1) micronodular cirrhosis in all patients; (2) diabetes mellitus in 75% to 80% of patients; and (3) abnormal skin pigmentation in 75% to 80% of patients.
- Iron accumulation in hereditary forms is lifelong but the injury caused by excessive iron is slow and progressive; hence *symptoms usually first appear in the fourth to fifth decades of life in men and later in women since menstrual bleeding counterbalances the accumulation until menopause.*
- Because many women do not accumulate clinically relevant amounts of iron within their lifetime, hereditary hemochromatosis affects more males than females (ratio of 5 to 7:1).

Pathogenesis. Because there is no regulated iron excretion from the body, the total body content of iron is tightly regulated by intestinal absorption. *In hereditary hemochromatosis, regulation of intestinal absorption of dietary iron is abnormal, leading to net iron accumulation of 0.5 to 1 gm/year.* The disease manifests itself typically after 20 gm of stored

Table 18-7 Classification of Iron Overload

I. Hereditary hemochromatosis
Mutations of genes encoding HFE, transferrin receptor 2 (TfR2), or hepcidin Mutations of genes encoding HJV (hemojuvelin: juvenile hemochromatosis) (Neonatal hemochromatosis)*
II. Hemosiderosis (secondary hemochromatosis)
A. Parenteral iron overload Transfusions Long-term hemodialysis Aplastic anemia Sickle cell disease Myelodysplastic syndromes Leukemias Iron-dextran injections
B. Ineffective erythropoiesis with increased erythroid activity β-Thalassemia Sideroblastic anemia Pyruvate kinase deficiency
C. Increased oral intake of iron African iron overload (Bantu siderosis)
D. Congenital atransferrinemia
E. Chronic liver disease Alcoholic liver disease Porphyria cutanea tarda
F. Neonatal hemochromatosis

*Neonatal hemochromatosis develops in utero and does not appear to be a hereditary condition.