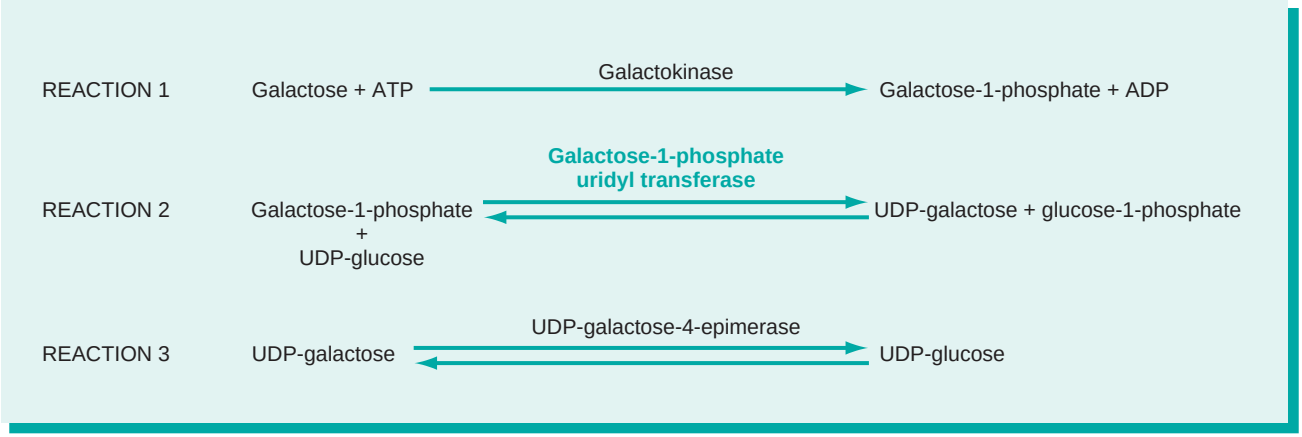

Figure 10-15 Pathways of galactose metabolism. ADP, Adenosine diphosphate; ATP, adenosine triphosphate; UDP, uridine diphosphate.

with milder disease. Moreover, some mutations result in only modest elevations of blood phenylalanine levels without associated neurologic damage. This latter condition, referred to as *benign hyperphenylalaninemia*, is important to recognize, because these individuals may well have positive screening tests but do not develop the stigmata of classic PKU. Because of the numerous disease-causing alleles of the phenylalanine hydroxylase gene, molecular diagnosis is not feasible, and measurement of serum phenylalanine levels is necessary to differentiate benign hyperphenylalaninemia from PKU; the levels in the latter are typically five-fold or more above normal. Once a biochemical diagnosis is established, the specific mutation causing PKU can be determined. With the identification of the mutation, carrier testing of at-risk family members can be performed.

While 98% of PKU is attributable to mutations in PAH, approximately 2% occur due to abnormalities in synthesis or recycling of the cofactor *tetrahydrobiopterin* BH_4 (Fig. 10-14). *It is clinically important to recognize these variant forms of PKU, because they cannot be treated by dietary restriction of phenylalanine.*

Galactosemia

Galactosemia is an autosomal recessive disorder of galactose metabolism resulting from accumulation of galactose-1-phosphate in tissues. Normally, lactose, the major carbohydrate of mammalian milk, is split into glucose and galactose in the intestinal microvilli by lactase. Galactose is then converted to glucose in three steps (Fig. 10-15). *Two variants of galactosemia have been identified. In the more common variant there is a total lack of galactose-1-phosphate uridyl transferase* (also known as *GALT*) *involved in reaction 2. The rare variant arises from a deficiency of galactokinase, involved in reaction 1.* Because galactokinase deficiency leads to a milder form of the disease not associated with mental retardation, it is not considered in this discussion. As a result of the transferase deficiency, *galactose-1-phosphate* accumulates in many locations, including the liver, spleen, lens of the eye, kidneys, heart muscle, cerebral cortex, and erythrocytes. Alternative metabolic pathways are activated, leading to the production of *galactitol* (a polyol metabolite of galactose) and *galactonate*, an oxidized by-product of excess galactose, both of which also accumulate in the tissues. Long-term toxicity in galactosemia has been variously imputed to these metabolic intermediates. Heterozygotes may have a mild enzyme deficiency but are spared the clinical and pathologic consequences of the homozygous state.

The clinical picture is variable, probably reflecting the heterogeneity of mutations in the galactose-1-phosphate uridyl transferase gene. The liver, eyes, and brain bear the brunt of the damage. The early-to-develop *hepatomegaly* is due largely to fatty change, but in time widespread scarring that closely resembles the cirrhosis of alcohol abuse may supervene (Fig. 10-16). *Opacification of the lens (cataract)* develops, probably because the lens absorbs water and swells as galactitol, produced by alternative metabolic pathways, accumulates and increases osmotic pressure. Nonspecific alterations appear in the CNS, including *loss of nerve cells, gliosis, and edema, particularly in the dentate nuclei of the cerebellum and the olivary nuclei of the medulla.* Similar changes may occur in the cerebral cortex and white matter.

These infants *fail to thrive* almost from birth. *Vomiting* and *diarrhea* appear within a few days of milk ingestion. *Jaundice* and *hepatomegaly* usually become evident during the first week of life and may seem to be a continuation of the physiologic jaundice of the newborn. The *cataracts* develop within a few weeks, and within the first 6 to 12 months of life *mental retardation* may be detected. Even in

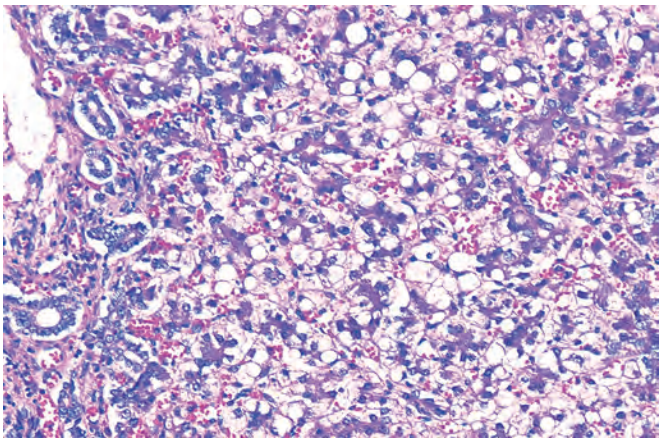

Figure 10-16 Galactosemia. The liver shows extensive fatty change and a delicate fibrosis. (Courtesy Dr. Wesley Tyson, The Children's Hospital, Denver, Colo.)