the physiologic basis of oral rehydration therapy for the treatment of diarrhea (Chap. 55). The mechanisms of intestinal fluid and electrolyte absorption and secretion are discussed in Chap. 55.

Although the intestinal epithelial cells are crucial mediators of absorption and of ion and water flow, the several cell types in the lamina propria (e.g., mast cells, macrophages, myofibroblasts) and the enteric nervous system interact with the epithelium to regulate mucosal cell function. Intestinal function results from the integrated responses and interactions of intestinal epithelial cells and intestinal muscle.

ENTEROHEPATIC CIRCULATION OF BILE ACIDS

Bile acids are not present in the diet but are synthesized in the liver by a series of enzymatic steps that also represent cholesterol catabolism. Indeed, interruption of the enterohepatic circulation of bile acids can reduce serum cholesterol levels by 10% before a new steady state is established. Bile acids are either primary or secondary. Primary bile acids are synthesized in the liver from cholesterol, and secondary bile acids are synthesized from primary bile acids in the intestine by colonic bacterial enzymes. The two primary bile acids in humans are cholic acid and chenodeoxycholic acid; the two most abundant secondary bile acids are deoxycholic acid and lithocholic acid. The liver synthesizes ~500 mg of bile acids daily; the bile acids are conjugated to either taurine or glycine (to form tauroconjugated and glycoconjugated bile acids, respectively) and are secreted into the duodenum in bile. The primary functions of bile acids are (1) to promote bile flow, (2) to solubilize cholesterol and phospholipid in the gallbladder by mixed micelle formation, and (3) to enhance dietary lipid digestion and absorption by forming mixed micelles in the proximal small intestine.

Bile acids are primarily absorbed by an active, Na^+-dependent process that takes place exclusively in the ileum; to a lesser extent, they are absorbed by non-carrier-mediated transport processes in the jejunum, ileum, and colon. Conjugated bile acids that enter the colon are deconjugated by colonic bacterial enzymes. The unconjugated bile acids are rapidly absorbed by nonionic diffusion. Colonic bacterial enzymes also dehydroxylate bile acids to secondary bile acids.

Bile acids absorbed from the intestine return to the liver via the portal vein and are then re-secreted (Fig. 349-1). Bile acid synthesis is largely autoregulated by 7α-hydroxylase, the initial enzyme in cholesterol degradation. A decrease in the volume of bile acids returning to the liver from the intestine is associated with an increase in bile acid synthesis/cholesterol catabolism, which helps keep the bile-acid pool size relatively constant. However, the capacity to increase bile acid synthesis is limited to ~2- to 2.5-fold (see below). The bile-acid pool size is ~4 g. The pool is circulated via the enterohepatic circulation about twice during each meal, or six to eight times during a 24-h period. A relatively small quantity of bile acids is not absorbed and is excreted in stool daily; this fecal loss is matched by hepatic bile-acid synthesis.

Defects in any of the steps in enterohepatic circulation of bile acids can result in a decrease in the duodenal concentration of conjugated bile acids and consequently in the development of steatorrhea. Thus, steatorrhea can be caused by abnormalities in bile acid synthesis and excretion, their physical state in the intestinal lumen, and reabsorption (Table 349-1).

Synthesis Decreased bile acid synthesis and steatorrhea have been demonstrated in chronic liver disease, but steatorrhea often is not a major component of illness in these patients.

Secretion Although bile acid secretion may be reduced or absent in biliary obstruction, steatorrhea is rarely a significant medical problem in these patients. In contrast, primary biliary cirrhosis represents a defect in canalicular excretion of organic anions, including bile acids, and not infrequently is associated with steatorrhea and its consequences (e.g., chronic bone disease). Thus, the osteopenia/osteomalacia and other chronic bone abnormalities often present in patients with primary biliary cirrhosis and other cholestatic syndromes are secondary to steatorrhea that then leads to calcium and vitamin D malabsorption as well as to the effects of cholestasis (e.g., bile acids and inflammatory cytokines).

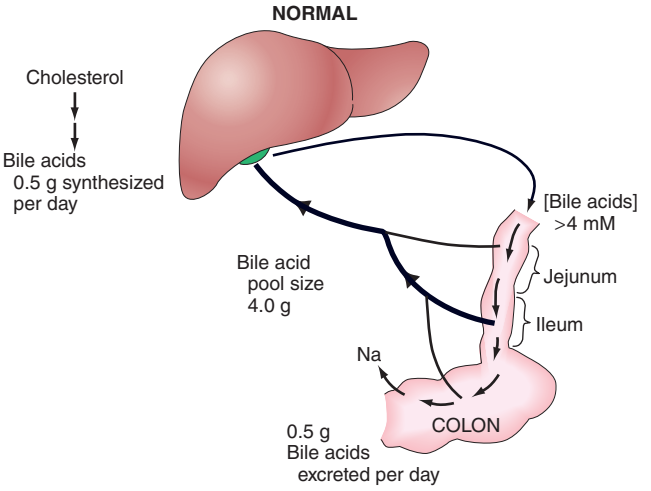

FIGURE 349-1 Schematic representation of the enterohepatic circulation of bile acids. Bile acid synthesis is cholesterol catabolism and occurs in the liver. Bile acids are secreted in bile and are stored in the gallbladder between meals and at night. Food in the duodenum induces the release of cholecystokinin, a potent stimulus for gallbladder contraction resulting in bile acid entry into the duodenum. Bile acids are primarily absorbed via an Na-dependent transport process that is located only in the ileum. A relatively small quantity of bile acids (~500 mg) is not absorbed in a 24-h period and is lost in stool. Fecal bile acid losses are matched by bile acid synthesis. The bile acid pool (the total amount of bile acids in the body) is ~4 g and is circulated twice during each meal or six to eight times in a 24-h period.

Maintenance of Conjugated Bile Acids In bacterial overgrowth syndromes associated with diarrhea, steatorrhea, and macrocytic anemia, a colonic type of bacterial flora is increased in the small intestine. Steatorrhea is primarily a result of the decrease in conjugated bile acids secondary to their deconjugation by colonic-type bacteria. Two complementary explanations account for the resulting impairment of micelle formation: (1) Unconjugated bile acids are rapidly absorbed in the jejunum by nonionic diffusion, and the result is a reduced concentration of duodenal bile acids. (2) The critical micellar concentration (CMC) of unconjugated bile acids is higher than that of conjugated bile acids; therefore, unconjugated bile acids are less effective than conjugated bile acids in micelle formation.

Reabsorption Ileal dysfunction caused by either Crohn's disease or surgical resection results in a decrease in bile acid reabsorption in the ileum and an *increase* in the delivery of bile acids to the large intestine. The resulting clinical consequences—diarrhea with or without steatorrhea—are determined by the *degree* of ileal dysfunction and the *response* of the enterohepatic circulation to bile acid losses (Table 349-2). Patients with limited ileal disease or resection often have diarrhea but not steatorrhea. The diarrhea, a result of stimulation of active Cl secretion by bile acids in the colon, has been called *bile acid diarrhea* or *choleretic enteropathy* and responds promptly to cholestyramine, an anion-binding resin. Steatorrhea does not develop because hepatic synthesis of bile acids increases to compensate for

TABLE 349-1 DEFECTS IN ENTEROHEPATIC CIRCULATION OF BILE ACIDS

Process	Pathophysiologic Defect	Disease Example
Synthesis	Decreased hepatic function	Cirrhosis
Biliary secretion	Altered canalicular function	Primary biliary cirrhosis
Maintenance of conjugated bile acids	Bacterial overgrowth	Jejunal diverticulosis
Reabsorption	Abnormal ileal function	Crohn's disease