Fig. 13.1. Physiologic processes involving bilirubin.

- In health, erythrocyte destruction within macrophages of the spleen, liver, or bone marrow is followed by the degradation of heme and its conversion to Bu. Small and usually clinically insignificant amounts of Bu are formed from heme degradation associated with ineffective erythropoiesis and degradation of other heme-containing molecules (catalase, peroxidase, and cytochromes). As Bu leaves a macrophage, it forms a noncovalent association with albumin (Alb) and remains associated with Alb until uptake by hepatocytes. Bu is relatively water insoluble prior to binding to Alb.
- When Bu enters the liver and its protein-permeable sinusoids, it enters hepatocytes without albumin and binds to Y-protein (ligandin, glutathione S-transferase B) or Z-protein (fatty acid–binding protein). Bu probably enters hepatocytes by a passive but facilitated process; binding proteins enhance the process by reducing the efflux of Bu back to the sinusoidal plasma.
- Within hepatocytes, Bu is conjugated with glucuronide (also glucose in horses) to form bilirubin monoglucoronide or bilirubin diglucuronide, collectively called Bc.
- Bc is transported from hepatocytes into canaliculi (the rate-limiting step in bilirubin excretion) by an energy-dependent transport system for organic anions other than BAs.
- Bc in bile enters the intestine and is degraded to urobilinogen (colorless). Urobilinogen can be passively absorbed in the intestine and then enter hepatocytes for excretion in bile, or bypass the liver and be excreted in urine. Urobilinogen can also be degraded to stercobilinogen (dark brown) and excreted in feces.
- If Bc escapes hepatocytes and enters the blood, it can pass through the glomerular filtration barrier and be excreted in the urine. Because Alb does not pass through the glomerular filtration barrier of most mammals, Bu/Alb does not enter the urine in those animals.

Bu/Alb, Bu associated with albumin; Mϕ, macrophage; Sb, stercobilinogen; Ub, urobilinogen; and UDP-G, uridine diphosphoglucuronide.

Fig. 13.2. Obstructive cholestatic icterus: Lesions of bile canaliculi or bile ducts (hepatic or posthepatic) inhibit bile flow, and thus less or no Bc is excreted to the intestine. Bc enters systemic blood because of (1) increased permeability of canalicular tight junctions and leakage to the space of Disse and the central vein, (2) hepatocyte necrosis allowing Bc entry to hepatic sinusoids, or (3) concurrent increased BA content that inhibits excretion of Bc to canaliculi and thus Bc is "regurgitated" to hepatic sinusoids. A persistently increased plasma [Bc] results in increased formation of Bδ and increased urinary excretion of Bc (bilirubinuria). Bu/Alb, Bu associated with albumin; Bδ, Bc covalently bound to albumin; Mϕ, macrophage; Sb, stercobilinogen; Ub, urobilinogen; and UDP-G, uridine diphosphoglucuronide.

Fig. 13.3. Physiologic processes of bile acids: Cholesterol is degraded in hepatocytes to a 1°BA, either cholic or chenodeoxycholic acid. A 1°BA becomes conjugated (usually with taurine or glycine, but sometimes with sulfate or gluconate) in hepatocytes to form a 1°BAc. A 1°BAc is secreted into the biliary system and transported via the bile ducts to the intestine. In the intestine, a 1°BAc has three possible fates: (1) absorption by the intestinal mucosa and entrance into the portal blood, (2) deconjugation by enteric bacteria to a 1°BA and then absorption by the intestinal mucosa and entrance into the portal blood, or (3) degradation to a 2°BA (either deoxycholic acid or lithocholic acid), which may have two fates—excretion in the feces or absorption by the intestinal mucosa and entrance into the portal blood. If conjugated with sulfate, BAs are poorly absorbed by the intestinal mucosa. When returned to the liver via the portal blood, conjugated BAs, deconjugated BAs, and 2°BAs are efficiently removed from the blood by the hepatocytes. The deconjugated BAs and 2°BAs are conjugated by hepatocytes and returned to the biliary system to complete the enterohepatic circulation. In health, nearly all BA molecules are within the enterohepatic circulation; very few are in the systemic blood. BA molecules that escape the enterohepatic circulation can be cleared from the plasma via glomerular filtration and excreted in the urine. 1°BA, primary bile acid; 1°BAc, conjugated primary bile acid; and 2°BA, secondary bile acid.

Fig. 13.4. Pathologic processes that increase serum [BA] (hypercholemia). Two major pathologic processes cause hypercholemia:

- Decreased clearance from the portal blood: The defect may occur because of (1) decreased uptake of BA from the sinusoidal blood because of a decreased functional hepatic mass or because (2) there is a portosystemic shunt.
- Decreased biliary BA excretion: When there is obstructive cholestasis (3) or functional cholestasis (4), the BAs are regurgitated to the sinusoidal blood instead of passing through the biliary ducts to the intestine.

Fig. 13.5. Physiologic processes of ammonium.

- Most NH_4^+ is produced in intestines by digestion of dietary proteins or by the metabolism of bacteria. Some NH_4^+ is produced by the deamination of amino acids (in many cells) and adenosine monophosphate (especially in muscle fibers).
- After NH_4^+ enters the liver (via the portal vein or the hepatic artery), it enters hepatocytes and is used for the synthesis of urea (in urea cycle), amino acids, and proteins. Urea diffuses from hepatocytes to the sinusoidal blood or the bile canaliculi, from which it may be excreted via the kidneys or the intestine, respectively. Urea that enters the intestine (from diet, bile, or blood) may be reabsorbed as part of an enterohepatic circulation (also see Fig. 8.5).
- Renal excretion of NH_4^+ may occur by NH_4^+ passing through the glomerular filtration barrier and being excreted in the urine. NH_4^+ is also fixed into urea in the hepatocytes or into glutamine (Gln) in the renal tubular cells. In response to acidemia, deamination of Gln to glutamate (Glu) in the renal tubules results in NH_4^+ excretion (see Fig. 9.6).
- NH_4^+ is the molecular form that is present in most aqueous body fluids at a pH of 7.4, but it does not diffuse through cell membranes. NH_3 is relatively lipid soluble and rapidly diffuses across cell membranes, but very little is present in body fluids.

Fig. 13.6. The urea cycle (Krebs-Henseleit cycle) in hepatocytes: The dashed structure represents a mitochondrion; the other reactions occur in a hepatocyte's cytoplasm. The roles of adenosine triphosphate (ATP) and phosphate are not shown.

- Carbamoyl phosphate synthetase (CPS) catalyzes the reaction in which NH_4^+ and HCO_3^- are used to produce carbamoyl phosphate. Ornithine carbamoyltransferase (OCT) catalyzes the combination of carbamoyl phosphate and ornithine to produce citrulline. Argininosuccinate synthetase (ASS) catalyzes the combination of citrulline with aspartate to form argininosuccinate (a link between the urea cycle and the citric acid cycle). Argininosuccinate lyase (ASL) catalyzes the generation of arginine and fumarate from argininosuccinate. Arginase catalyzes the combination of arginine and H_2O to urea and ornithine; ornithine is then available to begin the urea cycle again.
- Congenital deficiencies in ASS or OCT cause a defective urea cycle and hyperammonemia because NH_4^+ is not incorporated into urea.