Micelles formed in bile are a combination of BAs, CH, and phospholipids (PLs). The amount of CH dissolved in bile depends not only upon the biliary BA concentration, but also the amount of lecithin (PL) present, for it is the combination of BA and PL that provides the solvent capacity for CH. Gallstones in biliary passages usually form as either pigment stones (calcium salts of unconjugated bilirubin), or CH stones, and approximately 85% of CH stones have a bilirubin core. The answer is e.

7. Bile acid(s):

- **a. And CH synthesis in the liver are regulated by the enzymes HMG-CoA reductase, and 7-α-hydroxylase, respectively.**
- **b. Known as chenodeoxycholic (CDC) and cholic acid (CA) are secondary bile acids, formed by microbial action in the large intestine.**
- **c. Enterohepatic cycling is largely dependent upon an active transport step in the ileum.**
- **d. Are normally conjugated to glucuronides in the liver prior to biliary secretion.**
- **e. Are largely converted to coprostanol in the large intestine, which is the major fecal steroid.**

Approximately one-half of CH eliminated from the body is normally excreted in feces after conversion to BAs. The remainder is excreted as neutral steroids. Bile salts are Na^+ and/or K^+ salts of BAs. The two terms (bile salts or bile acids) are sometimes used interchangeably.

Coprostanol is the principal sterol in feces, but is formed from CH, not BA, in the lower intestine by bacterial flora. A large proportion (>95%) of biliary BA is normally reabsorbed by active processes in the terminal ileum. The BAs are immediately returned to the portal circulation, taken up by liver, and re-excreted into bile. This is known as the enterohepatic circulation (EHC) of BA, and is normally a highly efficient process. The BAs not reabsorbed (<5% of the circulating pool), or their derivatives, are normally excreted in feces.

Hepatic CH and BA synthesis are regulated by the enzymes HMG-CoA reductase and 7-α-hydroxylase, respectively. The activities of these two enzymes change in parallel, and consequently it is difficult to ascertain whether inhibition of BA synthesis takes place primarily at the HMG-CoA reductase step, or at the 7-α-hydroxylase step. Hepatic BA synthesis from CH results in the formation of two primary BAs, CDC, and CA. The ratio of these two varies with species, with CA predominating in primates, and CDC predominating in several domestic animals studied. The greater proportion of CDC in domestic animals may impart a greater protection against CH gallstone formation.

Primary bile acids (CDC and CA) are conjugated in hepatocytes to the amino acids taurine and glycine, thus forming glycocholate, taurocholate, glycochenodeoxycholate, and taurochenodeoxycholate. Conjugation imparts a greater water solubility to these molecules, making them less likely to precipitate in a watery medium like bile. Following biliary excretion, BAs and biliary CH are normally concentrated in the gallbladder (in animals having gallbladders). Bile acids that escape ileal reabsorption move into the large intestine where they may undergo microbial deconjugation and 7-α-dehydroxylation, forming the secondary bile acids, deoxycholate (from CA), and lithocholate (from CDC). These secondary bile acids are largely excreted in feces.

Some investigators believe that there is a higher incidence of colon cancer among humans consuming excessive amounts of red meat. One theory regarding this relationship holds that excessive amounts of CH are being converted to BA, increasing the BA pool. Increased amounts of BA thus enter the microbial-rich colon, where some BAs are converted to toxic (carcinogenic) steroid intermediates.

Clinically, hypercholesterolemia is treated by either inhibiting cholesterol biosynthesis (i.e., inhibiting HMG-CoA reductase), or by interrupting the EHC of BAs. Significant reductions in plasma CH can be affected by either or both procedures. Cholestyramine resin binds BAs in the intestine, thus interrupting their EHC. Then, because of release from feedback inhibition normally exerted by BAs in the EHC, the conversion of CH to BA is greatly enhanced in the liver in an effort to maintain the BA pool. This secondarily reduces the plasma CH concentration by enhancing hepatic removal of CH from the circulation for BA synthesis. The answer is c.

Endocrinology and Reproductive Physiology

SECTION VII