0031-6997/84/3601-0001$02.00/0
PHARMACOLOGICAL REVIEWS
Vol. 36, No. 1
Printed in U.S.A.

Mechanisms of Bile Formation, Hepatic Uptake, and Biliary Excretion

CURTIS D. KLAASSEN* and JOHN B. WATKINS III

Department of Pharmacology, Toxicology, and Therapeutics, University of Kansas Medical Center, Kansas City, KS 66103, and Medical Sciences Program, Indiana University School of Medicine, Bloomington, IN 47405

* Address correspondence to: Curtis D. Klaassen, Ph.D., Department of Pharmacology, Toxicology, and Therapeutics, University of Kansas Medical Center, Kansas City, KS 66103.

BILIARY excretion of xenobiotics is a complex process involving uptake into liver cells, intracellular sequestration and/or biotransformation, and transport into bile. A description of liver morphology and the possible mechanisms of bile formation is included to aid in the understanding of how chemical and physiological factors affect bile flow, hepatic uptake, and biliary excretion. Enterohepatic circulation interferes with the biliary elimination of xenobiotics from the body. The considerable volume of information that has accumulated in recent years on the mechanisms of bile formation, hepatic uptake, and biliary excretion is discussed in this comprehensive review.

I. Historical Aspects

Liver and bile have been considered to be important in determining temperament and health since the days of the ancient Babylonian and Greek civilizations. In Hippocratic medicine, bile was one of four cardinal humors (blood, phlegm, yellow bile from liver, black bile from stomach) which were thought to control the health status of the body. The Greek physician, Galen, main-

tained a humoral view of disease; for example, fevers of long duration were attributed to abnormalities in yellow and black bile. In fact, the word melancholy is derived from the Greek words, melas (black) and chole (bile) since mental depression was thought to arise from an excess of "black bile."

Scientific studies initiated by the seventeenth century anatomist and physiologist, Regnier de Graff, described the collection of bile and pancreatic juice from experimental fistulae. Then Schwann, in 1844, established the use of permanent biliary fistulae in dogs and Blondt, in 1846, was the first to use a cannula (378). Much work in the nineteenth century evaluated the physiological chemistry of bile and its composition. Crude preparations of bile salts were obtained by Thenard in 1807 and Berzelius in 1808, although the structures of the bile acids were not elucidated until the early 1930s (1259). Berzelius, in 1842, showed that bile pigment could exist in two forms, green-colored biliverdin and yellow bilirubin. By the 1890s, bile was considered to be a physiological secretion necessary for digestive processing of consumed fats as well as an excretory product containing cholesterol and bile pigments (378, 1027).

Today the dominant physiological role of bile is its involvement in digestion and the intestinal absorption of fats. However, studies on the excretion of numerous endogenous and exogenous compounds have demonstrated the importance of biliary excretion in the elimination of chemicals from the body. In his manuscript, Traité de Toxicologie Général (1813–1815), M. J. B. Orphila, the father of toxicology, noted that many metallic poisons are extracted by the liver and are either excreted into bile or remain in the liver. Later, Claude Bernard observed that copper sulfate, potassium iodide, and turpentine spirits are found in bile soon after intravenous administration. Then in 1866, Chrzonszczewsky developed a method to visualize the biliary tree based on biliary excretion of two dyes, aniline red and indigo carmine (189). These early studies were generally qualitative and the quantitative significance of hepatic extraction and excretion into bile remained obscure.

The demonstration in 1909 by Abel and Rowntree (1) that several phthalein dyes undergo extensive biliary excretion led to the development of diagnostic tests for hepatic and biliary function. The radio-opaque dye, tetraiodophenolphthalein, is excreted into bile and was used to visualize the gallbladder by X-irradiation (413). Meanwhile, Rosenthal and White (1002) introduced sulfobromophthalein (BSP) as a diagnostic test of liver function by measuring the rate of disappearance of the dye from plasma. BSP retention in plasma is an indicator of various forms of hepatic disease (724). Additional studies have been performed to determine mechanisms of hepatic disposition and biliary excretion of BSP and similar prototype chemicals.

The biliary elimination of xenobiotics was studied little during the first half of the twentieth century as work was directed toward understanding urinary excretion (1265). From 1950, with the wide-scale introduction of myriad synthetic chemicals (drugs, food additives, pesticides), the importance of bile as a channel of xenobiotic excretion was realized. Compounds of complex structure and higher molecular weight have a greater affinity for elimination into bile than chemicals of lower molecular weight. Thus, during the 1950s and 1960s, hepatic extraction of many diverse groups of xenobiotics was studied, including antibiotics, cardiac glycosides, azo dyes, steroids, and phenothiazines; the first review on biliary excretion was prepared by Smith in 1966 (1106).

II. Morphological Perspectives of Biliary Excretion

The liver receives blood from two different sources. Highly oxygenated blood carried by the hepatic artery and terminal hepatic arterioles and blood loaded with nutrients carried through the portal vein and terminal venules supply all structures in the portal tracts and the parenchyma (fig. 1). These two vascular affluents diverge throughout the liver and are accompanied by branches of nerves, biliary and lymphatic vessels, and fibrous tissue forming a complex known as the portal tract (hepatic triad). A second vascular tree originates with terminal hepatic venules (central vein) that converge to become the hepatic veins. Thus, blood flows from the spigot formed by confluence of the portal and arterial vasculature into the hepatic sinusoidal sink and then drains into the central vein. The space between the two vascular trees is filled with hepatocytes that line the sinusoids, which are arranged tridimensionally and burrow between hepatocytes, branching and anastomosing as they converge upon the terminal hepatic venule. Thus, the liver resembles an organized sponge with holes as the sinusoids and with walls of hepatocytes (117).

Several seemingly conflicting concepts of liver structure are actually complementary. The classic lobule in histological sections is hexagonal with portal spaces at each corner. The lobule can be viewed as a wheel with the central vein as the axle, the sinusoids as spokes, and the portal tracts lying on the circumference. Branches of hepatic artery, portal vein, lymph vessel, and bile ductule

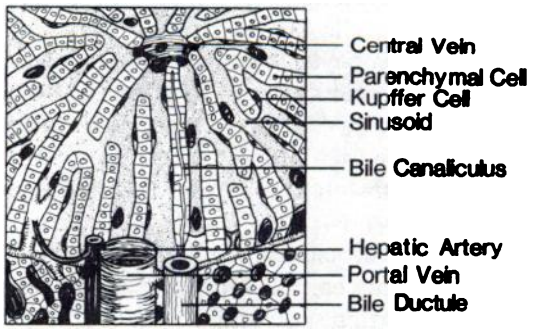

FIG. 1. Blood supply to liver by hepatic artery and portal vein.

are enclosed in a common vestment of connective tissue and course through the portal space. Blood enters the hepatic sinusoid from hepatic artery and portal vein, and flows centripetally through the lobule to exit via the central vein. This concept is somewhat misleading since central veins and portal tracts cross at all angles, but the lobule is seen only when adjoining central and portal veins are parallel and the tissue is sectioned at right angles to the axis of these vessels. However, the simple liver acinus was conceived as a microscopic parenchymal mass of irregular shape and size that is arranged around an axis formed by the portal triad (956, 957). The acini are not limited by any recognizable anatomical landmarks but extend outward to the terminal branches of one or more central veins. Interdigitation of terminal branches from three triangular portal spaces around one central venule creates a vascular pattern which, microscopically, resembles a hexagon. The parenchyma is continuous between adjacent acini and between classic lobules.

The sinusoids that separate the portal triad and central vein are larger than capillaries and more irregular in shape. They are lined primarily by a discontinuous matrix of endothelial cells lacking complete basal lamina and the branching pseudopodial Kupffer cell. These phagocytic cells normally lie on the luminal side but occasionally appear interposed between endothelial cells and form a minor portion of the sinusoidal wall. Intercellular gaps between endothelial cells, fenestrations, and lack of complete basal lamina permit blood plasma containing endogenous and exogenous substances to enter the space of Disse (fig. 2), i.e. between sinusoidal membrane and hepatocytes, and to have direct contact with the microvilli of the parenchymal cell membrane. Red blood cells cannot pass into the space of Disse.

The normal young adult rat has two main cell types, hepatic parenchymal cells and endothelial cells. Parenchymal cells constitute 90% to 95% of total liver weight but only 60% to 65% of total cell population, while reticuloendothelial cells (Kupffer, littoral, or sinusoidal cells) represent 5% to 10% of liver by weight and 35% to 40% of total cellular population (727). Phagocytic Kupffer cells remove and digest organisms and particulate matter that pass through the intestinal wall and enter blood. The hepatocytes (parenchymal or polygonal cells) are responsible for the elaboration of bile (460). The portion of the hepatocyte that abuts the sinusoids possesses microvilli that are bathed with extracellular fluid or plasma in the space of Disse. This structural arrangement facilitates contact between plasma protein-bound ligands and carriers on the surface of the hepatocyte membrane.

Whether using the classic lobule or the liver acinus concept, hepatocytes can be separated based upon distance from the vessels supplying blood (fig. 3). Cells in zone 1, or periportal region, are near the portal tracts

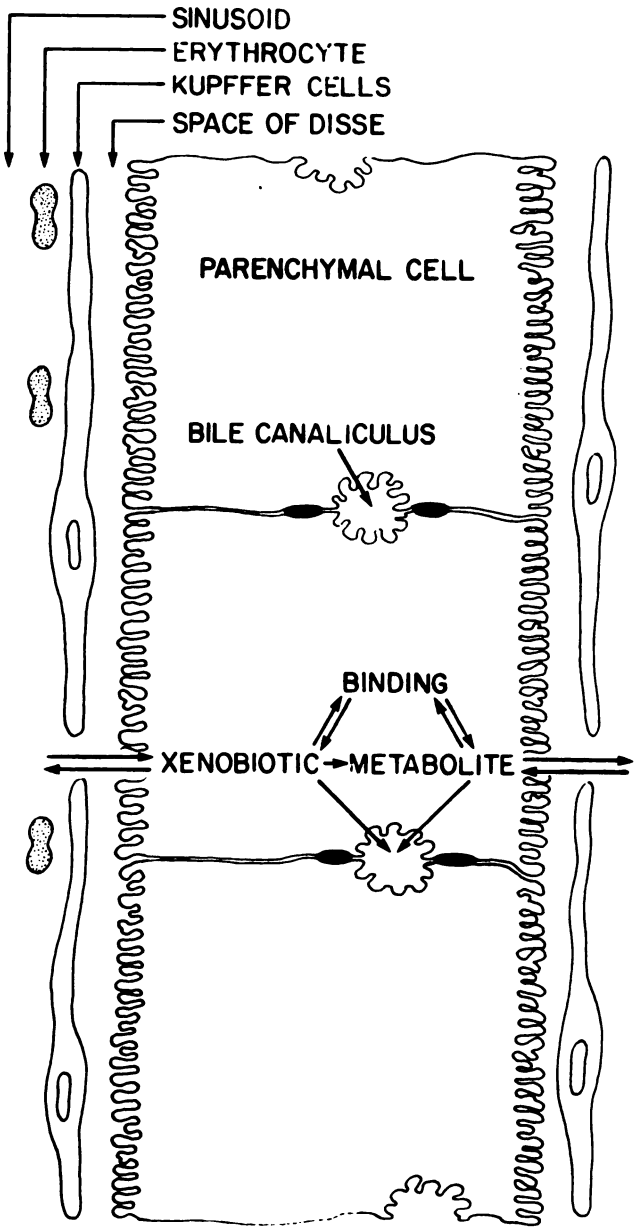

FIG. 2. Blood plasma enters space of Disse by intercellular gaps between endothelial cells, fenestrations, and lack of complete basal lamina.

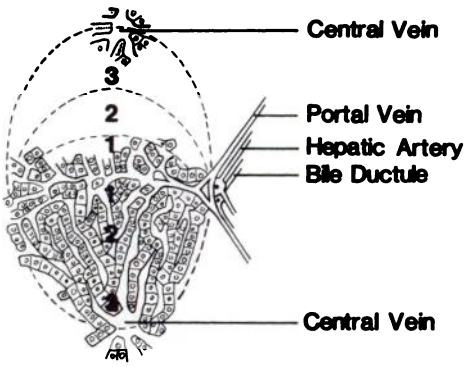

FIG. 3. Separation of hepatocytes based upon distance from vessels supplying blood.

and are bathed by blood closer in composition to arterial than to portal venous blood. Cells in zone 3, or centrilobular region, are in a zone in which no arteriole enters and are situated at the microcirculatory periphery around the central vein. Zone 2, or midzonal region, is a dividing layer of tissue between zones 1 and 3. Heterogeneity between centrilobular and periportal cells has been shown by histochemical studies (572, 859, 1223). Hepatocytes may be fractionated by centrifugation on Ficoll density gradients (166) into two classes: 1) light hepatocytes (mean density 1.10) are predominantly centrilobular and contain abundant smooth endoplasmic reticulum, numerous small mitochondria, and few glycogen granules; and 2) heavy hepatocytes (mean density 1.14) are primarily periportal and are characterized by large, compact glycogen granules and prominent rough endoplasmic reticulum (266, 441, 442, 1231). Centrilobular cells contain larger amounts of lysosomes and smooth endoplasmic reticulum than periportal hepatocytes (565, 754). In addition, bile canaliculi are larger in zone 1 than in zone 3 while those in zone 3 dilate more in response to bile acid-induced choleresis than canaliculi in zone 1 (719). Within the acinus, differences exist in oxygen tension, in rates of enzymes mediating protein synthesis, oxidation, hydrolysis and conjugation, and in concentration of glutathione (444, 1156). However, this functional heterogeneity does not result from differential expression of genetic properties inherent in hepatocytes but rather reflects quantitative differences in functional requirements.

There is a lobular gradient in the sinusoids as cells on the periphery of the lobule (zone 1 or periportal) are perfused first with blood containing higher concentrations of solutes while cells near the terminal hepatic veins (central vein, zone 3) are perfused last and exposed to blood with less solute. However, flow is not unidirectional because of the nonuniformity of resistances within the hepatocyte syncytium and the intermittent anastomoses of hepatic arterioles into zones 2 and 3. Compounds that diffuse through membranes will be concentrated in periportal cells, while solutes requiring a carrier will behave differently depending on the availability of transport systems. This lobular gradient of nonuniform exposure of liver cells to solutes has been illustrated for galactose (402), fluorescent dyes (445), and a bile acid derivative (563).

In addition to the labyrinthine sinusoids, the biliary system branches throughout the liver. Bile canaliculi are extracellular spaces as minute as 1 to 2 μm which are limited by, and located between, two or more abutting hepatocytes. The integrity of the biliary space is maintained by tight junctions that are stabilized by desmosomes and microfilaments (104, 375, 500, 862). Generally, a single canaliculus courses between adjacent cells and forms a tridimensional network of channels that conveys bile into larger ductules and eventually into bile ducts (ducts of Hering, or cholangioles) lined with cuboidal epithelium. The functional properties of bile ductules and ducts in bile secretion have not been determined (566). The apparent volume of the biliary tree in dogs is 2.5 μl/g of liver (75) and in rats, 2.3 (65, 452). The main duct from each lobe intersects forming the hepatic duct which anastomoses with the pancreatic duct to form the common bile duct which empties into the duodenum. Some species (rat, whale, and deer) do not have a gallbladder that branches off the hepatic duct.

III. Bile Composition

Composition of bile varies among species and upon the physiological and nutritional status of the animal at the time of bile collection. Table 1 indicates concentrations of biliary constituents in several species. Bile and plasma have similar electrolyte compositions; sodium is the dominant cation, while bile acids, chloride, and bicarbonate all contribute to total anion content. In addition, bile contains significant amounts of bile pigments, cholesterol, phospholipids, and protein. Relative concentrations of organic solutes and inorganic electrolytes may fluctuate but the osmolarity of bile is generally equivalent to that of plasma even when plasma osmolarity is artificially increased or decreased (1245). Average water content of bile is approximately 97%. Almost half of the 3% solid material is bile acids. In gallbladder bile, water content is lower (87%) which results from concentration of hepatic bile by the gallbladder.

Marked species differences occur in the relative amounts of the bile acid derivatives found in bile, the identity of the primary bile acid, and the nature of the conjugating group. These variations correlate roughly with diet; herbivores, except bovids, have primarily dihydroxy or monohydroxymonoketo bile acids conjugated with glycine, whereas carnivores have taurine conjugates of trihydroxy bile acids. Omnivores and bovids have significant amounts of all types (470). The rabbit and domestic pig excrete bile acids conjugated with glycine while humans eliminate both glycine and taurine conjugates of dihydroxy and trihydroxy bile acids. This dietary classification has exceptions such as the high proportion of taurocholate in rat bile (207, 469, 1244). Marked species variations occur also in phospholipid and cholesterol concentrations.

IV. Bile Formation

Production of bile by hepatocytes is a major, but poorly understood function of the liver. Bile formed at the canaliculi is modified in the ductules and ducts by processes of reabsorption or secretion of electrolytes and water. The study of hepatic bile formation is difficult because the primary secretion elaborated by hepatocytes is discharged into minute channels and cannot be sampled directly with current micropuncture techniques. Transmembrane ion fluxes and electrical potentials cannot be measured. Despite these anatomical limitations,

TABLE 1
Comparison of bile in different species.

Component	Rat*	Rabbit*	Dog*	Cat†	Guinea Pig†	Human‡
Na^+ (mEq/l)	162	170	166	163	156	146–155
K^+ (mEq/l)	6	4.2	5.5	4.2	4.4	2.7–4.9
Cl^- (mEq/l)	96	94	59	109	64	88–115
HCO_3^- (mEq/l)	25	45	42	24	72	27–55
Bile acid (mM)	38	35	20	26		3–45
Phospholipids (μg/ml)	412	58	1620			100–575
Cholesterol (μg/ml)	223	15	250			120
Protein (mg/ml)	6	2.1	11			0.3–3.0‖
Bile flow (μl/min/kg)§	65	82	5.6	13	160	3.6
Osmolarity (mOsmol/l)	332	312	293			

* Klaassen (632).
† Pugh and Stone (951).
‡ Thureborn (1178).
§ Cornelius (216).
‖ Russell et al. (1015).

much research has been conducted in recent years. Comprehensive reviews pertaining to mechanisms of bile formation are available and may be consulted for details of earlier work (124, 305–307, 309, 354, 556, 566, 570, 887, 970).

A. Osmotic Ultrafiltration

The central problem to understanding canalicular bile formation is comprehension of the mechanisms generating bulk movement of water into bile canaliculi. Possibilities include filtration, vesicular transport, and active transport of certain solutes leading to passive water flow.

In contrast to the kidney, the architecture of the liver does not provide an efficient arrangement for hydrostatic filtration. Bile is secreted against a pressure gradient that exceeds perfusion pressure in the isolated perfused rat liver (135). In addition, bile flow is independent of perfusion pressure and blood flow once a critical opening pressure is obtained and the oxygen supply to the tissue is not limited (136, 137). These results rule out hydrostatic pressure as an important determinant for bile production.

Another mechanism that may be operative in bile formation is the extrusion of materials by exocytosis. Horseradish peroxidase (978), lysosomal proteins (710, 711), immunoglobulin A (725), and insulin (228) are thought to be secreted into bile by a pathway involving the Golgi, associated lysosomes, and smooth endoplasmic reticulum (566). Although vesicular transport is demonstrated by the above examples, infrequent visualization of exocytic vacuoles suggests this excretory step does not contribute significantly to the formation of hepatocellular bile (354).

Present concepts of bile formation evolved from the initial hypothesis of Sperber (1114) that any osmotically active compound transported into bile can create an osmotic gradient from the hepatocyte into the canalicular lumen leading to passive movement of fluid from cells and/or intercellular spaces into the lumen. Bile will continue to flow if solute is transported into the canaliculi, providing that resistance to flow in the biliary tree does not exceed the osmotic pressure created by transported solute(s).

Canalicular bile formation is estimated indirectly by measuring the biliary clearance of inert solutes, whose elimination is not significantly modified by processes in bile ductules and ducts, that enter the bile at the canaliculi by simple, nonrestricted diffusion. The solutes, erythritol and mannitol, have been thought to meet these requirements. Hepatocytes are remarkably permeable to erythritol and mannitol (353, 392, 897), and their excretion depends on the permeability of the epithelium and the rate of bile flow at a specified locus (350, 351, 353, 356, 1245). Clearances of erythritol and mannitol correlate with changes in bile flow during bile acid-induced canalicular choleresis. However, recent studies in dogs and rhesus monkeys suggest that secretin, which induces ductular bile production, also stimulates erythritol and mannitol clearance (61, 74, 737). The transfer of erythritol, sucrose, and inulin from plasma to bile across isolated perfused duct segments from rats is proportional to molecular size (1105). Accurate determination of the magnitude of canalicular bile formation may also be affected if back diffusion of solutes occurs. Although the validity of erythritol as a measurement of canalicular bile production has been questioned (256, 737, 1105), its clearance provides the only quantitative estimate of canalicular bile production presently available.

B. Bile Acid-dependent Flow

In 1890, Schiff demonstrated that feeding bile to dogs with biliary fistulas produced a choleresis. In fact, a direct relationship between bile acid excretion and biliary flow has been observed in all species examined, including humans, over a wide range of bile acid excretion rates (125, 127, 630, 938, 1148). Bile acids are among the most effective choleretic agents (1246) and bile formed by their active secretion is known as bile acid-dependent flow. Studies in the dog (940, 1253), guinea pig (1080), and

pony (37) indicate that bile flow rate is directly proportional to the rate of sodium taurocholate excretion after intravenous infusion over a wide concentration range.

Normally, bile acids are present in bile as mixed micelles (161), and their osmotic activity in bile is generally less than that of nonassociated molecules. Dehydrocholic acid does not form micelles and produces choleresis at a lower concentration than does micelle-forming cholic acid (1116). Although a single micelle has a similar osmotic activity as 1 molecule of free bile acid, its effective osmotic pressure is greatly reduced by formation of large polyanionic aggregates with a molecular weight of about 27,000 (556). Each micelle contains around 500 bile acid molecules.

However, canalicular bile is not produced completely by the osmotic properties of bile acids. Interruption of the enterohepatic circulation markedly decreases bile acid excretion but has little effect on bile flow (623). Conflicting data for dehydrocholate-induced choleresis indicate that the increase in bile flow precedes the excretion of dehydrocholate by more than can be accounted for by the biliary tree dead space (1109). Bile flow associated with secretion of micelle-forming cholate may actually exceed that associated with non-micelle-forming taurodehydrocholate (875). Attempts to correlate choleretic properties with micelle-forming capacities of bile acids in vitro have failed (37, 630, 876, 1067). The bile acid-dependent fraction has also been proposed to result from osmotic activity of inorganic cations that accompany anionic bile acids to maintain electrical neutrality. The osmotic activity of a solute depends on the relative permeability of the membrane to solute as compared to solvent, or its reflection coefficient (566). Reflection coefficients of the biliary tree for different solutes are unknown due to the technological inability to sample bile at the canaliculus. Bile acid-dependent flow may also originate from some modulatory effect of bile acids on transport systems for other osmotically active solutes such as sodium ion (632, 928, 1230).

C. Bile Acid-independent Flow

Although hepatocellular bile formation was originally believed to be due to the osmotic activity of bile acids, linear extrapolation of the regression line for bile flow versus bile acid excretion to the ordinate indicates canalicular secretion in the absence of bile acid excretion (fig. 4) (1254). This bile is termed the bile acid-independent fraction and has been observed repeatedly in many species including dogs, rats, rabbits, and humans (102, 125, 251, 311, 938, 958, 1148, 1254). In contrast, chickens produce only small amounts of bile that are independent of bile acid secretion (157). However, representation of the bile flow versus bile acid excretion relationship by a single regression line may not be valid since infusion of bile acids into bile acid-depleted rats or rhesus monkeys results in a family of regression lines which progressively diminish in slope as the biliary bile

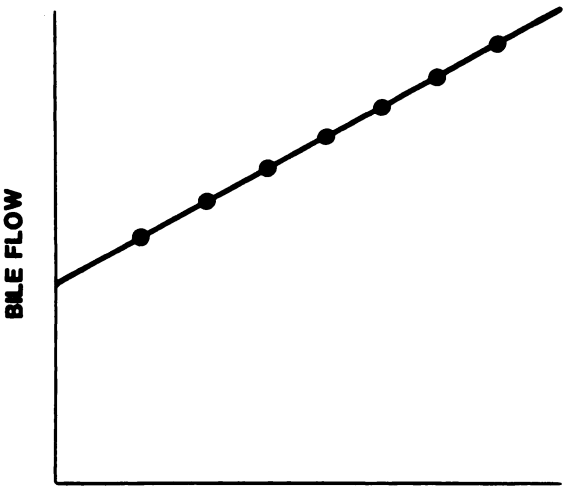

FIG. 4. Linear extrapolation of bile flow versus bile acid excretion.

acid concentration increases (52, 58). At low bile acid concentrations (< 10 mM), the slope of the regression line is approximately 10 times that found at higher levels (35 to 45 mM). Thus, the osmotic activity of bile acids is relatively greater at lower concentrations, and calculation of the bile acid-independent fraction of bile flow by linear extrapolation of bile flow versus bile acid secretion at concentrations above 10 mM might overestimate this fraction.

The bile acid-independent fraction of canalicular bile secretion varies among species (309) and comprises 40% of spontaneous basal bile secretion in humans (742) and about 60% in lagomorphs and rodents (311, 623, 1080). In addition, pretreatment with phenobarbital for 4 days increases bile formation by 50% in the rat but does not stimulate bile acid excretion (102, 622, 623). Other studies in the isolated perfused rat liver demonstrate definite secretory pressures even with negligible bile acid secretion (127).

1. Sodium Ion Secretion. The mechanism for formation of the bile acid-independent fraction is not known but may be due to sodium, chloride, or bicarbonate ion excretion. Sodium ion secretion has been implicated by two separate lines of evidence. First, cyclic 3′,5′-adenosine monophosphate (cAMP) increases sodium ion transport out of the hepatocytes and stimulates bile flow in the dog by increasing bile acid-independent flow (885). Glucagon and theophylline, which increase intracellular cAMP levels, also stimulate this fraction of bile flow in dogs (70, 567). In addition, theophylline increases bile acid-independent flow in rats but does not increase net bile flow because the bile acid-dependent fraction is decreased (674). In the rat, glucagon and dibutyryl-cAMP do not stimulate bile flow (51). In fact, Poupon et al. (933) examined the effects of dibutyryl-cAMP, aminophylline, and glucagon on bile acid-independent flow in the dog and rat and found no relationship between 1) the accumulation of cAMP or 2) the magnitude of the

rise in cAMP, and the increase in bile flow. They concluded cAMP does not have a physiological role in bile formation. Whether other cyclic nucleotides, such as cyclic guanosine monophosphate, are cellular mediators of secretion is unknown, but reductions in extracellular calcium ion markedly inhibit bile production in isolated rat liver (889). Thus, an interrelationship between cyclic nucleotides, calcium fluxes and bile secretion cannot be excluded.

Second, modulation of sodium ion excretion by controlling Na^+-K^+-adenosine triphosphatase (ATPase) activity is thought to influence the formation of this fraction of bile flow. Na^+-K^+-ATPase was implicated when inhibitors such as amiloride, ethacrynic acid, and ouabain diminished the bile acid-independent fraction in rabbits (310, 311). In contrast, later studies indicated ethacrynic acid produces choleresis in rabbits and rats (178, 658, 1078), and ouabain increases bile flow in rats (410, 1017). Graf and Peterlik (412) suggested that the choleretic effect of ouabain in the isolated perfused rat liver results from inhibition of sinusoidal Na^+-K^+-ATPase. The consequential rise in intracellular Na^+ concentration would stimulate the canalicular ATPase to extrude more sodium ion thereby increasing canalicular bile flow. However, unaltered ouabain (1017) and the glutathione conjugate of ethacrynic acid (178, 658) are readily concentrated in bile, and choleresis is attributable to an osmotic effect of the drugs themselves. Recent evidence suggests both mechanisms may be important in that canalicular excretion of the glutathione conjugate is rate-limiting but is accompanied by enhanced extrusion of Na^+ into the canalicular lumen (908). Others indicate that vasoconstrictive actions of cardiac glycosides might account for the reduction in bile acid-independent flow (812, 1162, 1177).

The affect of numerous compounds on bile formation [rose bengal (704), ethinylestradiol (968), phenobarbital (968, 1091), taurocholate (1230), thyroid hormones (717), ethanol (762), and cycloheximide (747)] has been attributed to influences on Na^+-K^+-ATPase supposedly present at the canaliculi. However, recent evidence demonstrates that Na^+-K^+-ATPase is located on the sinusoidal and lateral surfaces of the hepatocytes (113, 715, 934). Alterations in bile acid-independent flow and Na^+-K^+-ATPase activity do not always change in parallel (595, 796). Thus, generation of this fraction of bile flow may not depend on Na^+-K^+-ATPase activity; instead the major ATP-hydrolyzing enzyme at the biliary pole of the hepatocyte has been suggested to be Mg^{++}-ATPase (317, 478, 509).

Alterations in liver plasma membrane fluidity directly affects Na^+-K^+-ATPase activity. Fluidity has been increased in rats pretreated with propylene glycol, thyroid hormone, and cortisone, decreased by ethinylestradiol, and unaffected by phenobarbital (595). The role of membrane fluidity in bile formation needs further study. Recently, a method for isolating canalicular-enriched plasma membranes has been reported (1033). The membranes exist as vesicles and are highly enriched in alkaline phosphatase, Mg^{++}-ATPase and 5′-nucleotidase. Physiological concentrations of micelle-forming bile acids reversibly inhibit both Mg^{++}- and Na^+-K^+-ATPases and reversibly increase the fluidity of liver plasma membranes in vitro (1034). Although there are many data on the enzymatic and transport properties of the ATPase (994), more information is needed before their role in bile formation is understood (308).

Recent studies in isolated perfused rat liver where sodium ion is completely replaced by lithium ion indicate that much of the basal bile acid-independent bile formation is probably attributable to an ion pump other than Na^+-K^+-ATPase (1202). Although Na^+-K^+-ATPase activity is depressed, bile acid-independent flow is not influenced by complete replacement of sodium ion, thus suggesting that other mechanisms mediate elaboration of this fraction of bile.

2. Chloride and Bicarbonate Ion Secretion. Transport of anions other than bile acids may influence formation of the bile acid-independent fraction. Replacement of chloride ion in the perfusate of the isolated rat liver with nitrate ion decreases bile flow by 20% (411). After readmission of chloride ion, bile flow returns to normal thus indicating that transport of chloride ion may be a minor determinant of secretion. Since bile is alkaline with respect to plasma by virtue of its bicarbonate ion content, transport of this ion may be more important. Hardison and Wood (465) observed a reduction in bile flow and sodium ion excretion when bicarbonate ion was removed from the perfusate while bile acid elimination was unaffected. Bile flow rates were restored to control values upon addition of bicarbonate or dimethyloxazolidine-2,4-dione, a weak, membrane-permeable acid capable of transporting protons (465). Thus, bicarbonate transport in the liver may involve a sodium-hydrogen exchange system where CO_2 diffuses across the membrane, hydrates, and ionizes to $H^+ + HCO_3^-$. A proton is supplied for Na^+-H^+ exchange diffusion and bicarbonate ion is apparently transported into bile. Similar carrier systems have been well characterized in the renal tubule (388, 846), pancreas (1046, 1155), and small intestine (1192). Choleresis induced by SC-2644 in the dog is due to stimulation of canalicular bicarbonate secretion (72, 387). The peptide hormone secretin produces choleresis in the dog which is associated with an increase alkalinity of bile and total excretion of HCO_3^- (568, 940). Erythritol clearance measurements suggest the secretin-induced choleresis is of ductular rather than canalicular origin. However, secretin has no effect on bile flow or composition in the rat (309), yet Hardison and Wood (465) demonstrated a role of bicarbonate ion in bile formation in that species. Whether bicarbonate transport contributes to bile flow of canalicular or ductular origin remains

uncertain. Recent studies in cultured hepatocytes indicate that sodium-coupled chloride transport may be important in the production of bile acid-independent flow (1037). However, no definitive evidence was presented to suggest that chloride transport accounts for a major portion of basal bile flow.

3. Paracellular Fluid Flow. Bile may also be formed via the paracellular pathway where water and inorganic solutes gain entrance into bile through the intercellular spaces and associated junctional complexes (126, 297, 720). Considerable electrophysiological evidence demonstrates certain epithelia with low electrical resistance (i.e., the jejunal epithelium) are "leaky" and their tight junctions permit passage of fluid (370). Hepatocyte junctions have been classified as intermediate between tight and leaky based on the number of associated microfilaments (365, 782). However, these structures appear to be heterogeneous which may be important in the regulation of functional permeability (702). Layden et al. (720) demonstrated that dehydrocholate infusion increased 1) bile flow, 2) biliary clearance of [^{14}C]sucrose, an index of membrane permeability, and 3) incidence of invaginations of the intercellular surface membranes adjacent to the junctional complexes of hepatocytes. Similar morphological changes were observed after chronic taurocholate infusion (844). Metz and Bressler (803) noted that the morphological changes in tight junctions induced by bile duct ligation were reversible following reestablishment of the enterohepatic circulation. These data suggest that hepatocyte tight junctions are not static structures but may respond to alterations in bile flow. Additional evidence indicates that phalloidin treatment increases the permeability of the junctional complex which controls the barriers to paracellular fluid flow (297).

Paracellular ion equilibration could occur at two sites: between hepatocytes and/or in bile duct epithelia. Since the surface/volume ratio of the biliary tree decreases abruptly at the canaliculi-portal ductule junction, osmotic equilibration in ductules or ducts is unlikely (354). Bile osmolarity is similar to that of red blood cell-free perfusates (150 to 450 mOsmol/l) in isolated perfused rat liver thereby indicating that bile must attain osmotic equilibrium at the hepatocyte (124) because bile ducts are functionally inactive and do not permit exchange of ^{24}Na or ^{36}Cl (411). The permeability barrier to ion entry depends on ion species. The sequence for cations is lithium > sodium > potassium > Tris > choline, and for anions is nitrate > chloride > acetate > sulfate. Graf and Peterlik (411) concluded these ions enter bile by crossing the junctional complex from blood to bile.

Selective permeability of the biliary canalicular membrane has been evaluated by measuring the clearance of charged and uncharged weight-matched solute pairs ([carboxyl-^{14}C]inulin and [methoxy-^{3}H]inulin, and [^{14}C] ferrocyanide and [^{3}H]sucrose) (130). Since the molecular dimensions and diffusion abilities are similar, the lower biliary clearance for the negatively charged species suggests there is an electrical barrier to anion movement. Solute pair clearance ratios were constant over changing bile acid excretion rates thus implying that bile acids did not generate a significant negative potential in the canalicular lumen. Clearance of methoxyinulin and the much smaller molecule sucrose were similar, suggesting identical channels for both solutes which are much larger than the pores that admit water and smaller solutes such as erythritol. Bradley and Herz (130) estimated these channels represent 10% of the surface area available for water movement.

4. Microfilaments and Microtubules. Microfilaments associated with actin are found in hepatocytes (363) at the cytoplasmic face of the plasma membrane, particularly around canaliculi where a thin network extends into the microvilli (375, 862). Microfilaments derive from the globular protein actin and are responsible for the contractile functions of many cells. Phalloidin causes irreversible polymerization of actin into microfilaments thus producing hyperplasia of actin filaments in hepatocytes and a decreased bile flow (268, 297, 374, 408, 1189). Cytochalasin B specifically inhibits the contractile function of microfilaments and produces a thickening of microfilaments within the pericanalicular ectoplasm, a loss of microvilli from bile canaliculi, and a decreased bile flow in the perfused rat liver (919).

Microtubules consist almost exclusively of polymeric tubulin. Colchicine, an inhibitor of tubulin polymerization, causes an almost complete disappearance of microtubules and decreases bile acid secretion (269). Colchicine also inhibits secretion of lipoproteins and proteins into the serum (269, 1130). Combined administration of phalloidin and colchicine synergistically increases the pericanalicular microfilamentous network and the disappearance of microtubules and decreases basal bile flow (269). Agents that decrease microtubular function, such as vinblastine, vincristine, and colchicine, also cause hepatic accumulation of small secretory vesicles containing proteins and triacylglycerol which are normally excreted into bile (232, 942, 960). Two benzimidazole carbamates, nocadozle and parbendazole, with antimicrotubular activity block the biliary secretion of albumin and triacylglycerol by isolated hepatocytes (108); this indicates involvement of microtubules in biliary protein excretion.

Microtubules and microfilaments also play a role in bile acid uptake by isolated hepatocytes (965) and in biliary lipid secretion (419). In fact, rat hepatocytes in primary culture show dynamic contractions of bile canaliculi by actin-containing microfilaments which may influence bile production (920).

D. Ductular Modification of Canalicular Bile

The ductular-ductal system can alter electrolyte composition and volume of canalicular bile by reabsorption and/or secretion of water. Secretion of water depends on

active bicarbonate excretion (177, 350, 1148) and possibly an electroneutral sodium chloride pumping mechanism (105). The quantitative contribution of ductular secretion to total bile flow is highly species-dependent. Intermittent feeders, such as dogs and humans, have an important ductular component, while continuous eaters, such as most rodents, have a negligible contribution of the collecting system to bile flow (354). The concentration ratios of erythritol in bile to plasma are as follows: dog, 2.3; rabbit, 1.2; rat, 0.9; and guinea pigs, 0.7 (311, 350, 356, 623, 632, 1254). These data indicate considerable ductular reabsorption in dogs, some in rabbits, no reabsorption in rat, and some ductular secretion in guinea pigs. The ratio in humans is between 0.27 and 0.43, indicating pronounced ductular secretion (125, 743, 938). Rodents have high rates of spontaneous bile flow (50 to 90 μl/min/kg) and large bile acid-independent fractions.

Many gastrointestinal hormones, which exert physiological control of gastric acid secretion, intestinal motility, and gallbladder contraction, can also influence bile composition and volume during eating and digestion and hence affect the choleretic properties of these hormones and the enterohepatic cycle of bile acids. Studies of controlled interruption of the enterohepatic circulation (261) and comparison of fed versus fasted state on bile production in primates (1150) emphasize the importance of eating on variations in ductular secretion.

The best evidence for ductal modification of canalicular bile is that the pancreatic peptide secretin stimulates bile formation in isolated bile ducts of dogs (832) thus producing an abrupt negativity in the lumenal membrane potential indicative of active anion transport, possibly HCO_3^-. In addition, analysis of excretory transients after selective arterial injections of secretin support a ductular site of action (1251). Bile becomes slightly hypertonic during secretin choleresis (940) which probably results from increased excretion of chloride and bicarbonate ions (463).

Reabsorption and secretion of water and electrolytes can be performed by ductular epithelium, especially after cholinergic blockade in dogs (1254) and resection of the antrum and small bowel in monkeys (1148); both procedures suppress hormone-mediated secretion. A constant amount of water is reabsorbed during taurocholate-induced choleresis (74), suggesting that fluid reabsorption occurs independently of bile flow. In dogs, the concentrative capacity of the common bile duct increases after cholecystectomy (1253). After surgery and an overnight fast, extrahepatic ducts are enlarged and contain several milliliters of bile similar in composition to gallbladder bile. Ductal reabsorption appears to be independent of canalicular bile production in dogs and monkeys and is almost non-existent in rats and rabbits (354, 367, 632, 970). The reason for this species difference is unknown. Additional evidence indicates the ducts in rats and humans may actively reabsorb glucose (447, 872, 873) and slowly reabsorb urea (911). Retrograde intrabiliary injection experiments indicate extensive absorption of water, morphine, and BSP. The latter two undergo subsequent conjugation and biliary excretion (371, 534, 872, 873, 911–913). Whether secretion or reabsorption predominates under normal physiological conditions, however, is unknown.

E. Neurohumoral Control of Bile Formation

There are numerous factors that influence bile flow but whose sites of action are unknown (306, 307, 309, 354, 570, 970). These factors include neural influences, vascular pressure, and hormones.

Nerve fibers are abundant within the portal tract blood vessels, bile ductules, and ducts (359, 1152). Whether these nerves influence bile flow directly has not been determined. However, alterations in hepatocellular perfusion induced by nerve stimulation could influence bile formation by affecting the counterflow arrangement (1135). A direct effect of vagal tone on bile flow has been suggested since truncal vagotomy decreases spontaneous bicarbonate secretion and reduces insulin-induced choleresis (407, 579). Apparently, considerable species differences exist as stimulation of the vagus influences bile flow in man (60) and dogs (367, 383, 579, 924, 1161) but has no effect in rabbits and cats (1161). Although choleresis is observed after dopamine administration (468), adrenergic control mechanisms are even less understood than are vagal effects. It is also difficult to discern whether these effects result directly from neurotransmitters or from indirect neural influences mediated by alterations in perfusion, released hormones, and/or metabolic changes.

Bile flow is largely unaffected by variations in hepatic blood flow rate once a critical opening pressure is attained (136, 137). In contrast, released hormones can produce marked changes in bile flow (354, 570, 970). For example, gastrin (1294) and histamine (582) stimulate production of bile with high bicarbonate and chloride ion concentrations, respectively. Gastrointestinal hormones that stimulate flow are listed in decreasing order of potency: cholecystokinin, caerulein, pentagastrin, and gastrin II (569, 578, 580). Sulfated gastrin II, but not gastrin I, is choleretic only at pharmacological—not physiological—doses (578). Feeding also increases bile flow (568).

Hydrocortisone increases flow of hepatocellular bile with a high chloride ion concentration in dogs (759). Like insulin, glucagon also stimulates bile flow in man (282, 730) and dogs (581), but not in guinea pigs and rabbits (1079), by apparently increasing cAMP levels. Whether glucagon stimulates canalicular or ductular bile flow has not been determined. Thyroidectomy and hypophysectomy decrease bile flow (623, 717). Thus, numerous hormones have profound actions on the elaboration of bile and biliary flow by mechanisms yet to be elucidated.

Bile flow, biliary concentrations, and excretion rates of bile acid, cholesterol, and phospholipid follow a circadian rhythm in rats with a peak at midnight and a nadir at noon (57, 59, 267, 491, 1214). Bile acid-independent flow is maximal during the night and early morning (57, 59). Biliary transport maximum for dibromophthalein disulfonate (DBSP) was 25% higher at night than at noon (1214, 1217). In addition, food intake stimulates bile flow and appears to be a major factor in the circadian rhythm of bile secretion (801).

V. Alteration of Bile Formation

Many endogenous compounds and xenobiotics increase or decrease bile flow and are referred to as choleretic and cholestatic agents, respectively. Bile flow rate may be expressed relative to body weight or liver weight (usual methods) or hepatic DNA content (811).

A. Choleresis

A chemical can increase bile flow by stimulating the manufacture and secretion of biliary constituents and by biliary excretion of the chemical and/or its metabolites.

1. Bile Acids. The acute effect of bile acids on bile production has been extensively examined. Presumably, choleresis results from the osmotic gradient created by excretion of bile acids into the canalicular lumen. Recent studies in rats indicate the following choleretic potencies in decreasing order: dehydrocholic acid > chenodeoxycholic acid ≥ cholic acid > taurocholic acid > deoxycholic acid > glycocholic acid (337, 877). Similar results have been observed in dogs (624, 630). The volume of water excreted per micromole of bile acid (estimated by calculating the slope of the relation between bile flow and bile acid excretion; fig. 4) depends on species and bile acid.For taurocholic acid it is 8 μl in dogs (940, 1254), 13 μl in rhesus monkeys (261), 15 μl in rats (102, 1080), 30 μl in rabbits (310), and 26 μl in guinea pigs (1080). In the rat and rabbit, bile acids can produce a two- to threefold increase in bile flow while in the dog they increase bile flow six- to sevenfold (624). These differences are largely due to the much lower basal bile flow in dogs. Dehydrocholate produces a higher bile flow which is thought to be related to its lower tendency to form micelles (243, 1080, 1114) since the osmotic potency of micelle-forming bile acids is lower than that of non-micelle-forming bile acids (461). More recent studies suggest that the choleretic potency of bile acids is not inversely related to their ability to form micelles (337, 630, 875, 1067).

The bile flow during bile acid choleresis often exceeds that which would be theoretically accounted for by simple osmotic activity of the bile acid in bile. This extra bile may be formed either by effects on an electrolyte pump or by decreased reabsorption of fluid from the biliary tract. Wheeler et al. (1254) showed that bile flow would increase by only 1 to 2 μl/min/kg if fluid reabsorption were inhibited. Thus, the most likely explanation is that bile acid-independent flow may also be stimulated by bile acids (635).

Another factor important in determining differences in bile acid-induced increases in bile flow is the permeability (conductivity) of the canalicular epithelium to water and inorganic ions. This factor is thought to be the most important determinant of interspecies variations in bile flow (1246, 1247), but probably does not represent a major mechanism for bile acid choleresis (875). A recent study has shown that 7-ketolithocholate and ursodeoxycholate stimulate bile flow of canalicular origin which is rich in bicarbonate (277). Since bile flow exceeded the theoretical value for an osmotic choleresis and since bicarbonate excretion was elevated, these two bile acids apparently stimulate bile flow by at least two mechanisms.

2. Other Organic Compounds. Numerous xenobiotics including organic anions, cations, and neutral compounds are capable of producing a choleresis in one or several species of animals. Basal bile flow rate varies widely from 5 μl/min/kg in dogs to 60 in rats and rabbits, and 160 in guinea pigs (428, 624, 951), and the choleretic effect of a xenobiotic partly depends on the species and its basal flow. For example, bile flow is increased twofold in rats and rabbits and six-fold in dogs by cholic, taurocholic, and dehydrocholic acids (624). In general, BSP, eosine, fluorescein, ioglycamide, phenol red, and phlorizin are choleretic and increase bile production by the osmotic activity of the chemical in bile (309). However, the effect of these compounds on bile flow is dose-dependent. For example, low doses of BSP produce choleresis in dogs (493), but higher doses in rats (948) and mice (428) are cholestatic.

Several xenobiotics such as probenecid (314), ethacrynic acid (178, 658), diethyl maleate (73), iodipamide (342), iodoxamate (96, 329), ioglycamide (750), 1-chloro-2,4-dinitrobenzene-5-glutathione (1225), BSP-glutathione (71, 340), dihydroxydibutyl ether (215), valproic acid (252, 253, 1234, 1236), naltrexone (995), 6,7-dimethylesculetin (1158), and genipin and patrinoside (1159) stimulate bile flow in rats or dogs. Choleresis induced by these compounds occurs immediately after acute administration and is predominantly due to the osmotic activity of the compound and/or its metabolites. However, the volume excreted per microequivalent of chemical exceeds the theoretical maximal increment in bile flow (7 μl/μmol) anticipated for most of the above xenobiotics (diethyl maleate, 13 μl in rat and 17 μl in dog; iodipamide, iodoxamate, and ioglycamide, 22 μl; valproic acid, 16 μl). Values for BSP-glutathione and taurocholate are 16 and 7 to 14 μl/μmol, respectively (71, 493, 1080). Apparently, other determinants of canalicular secretion are also stimulated.

Other substances that induce choleresis by stimulating bile acid-independent flow include theophylline and cAMP (70), hydrocortisone (276, 759), thyroxine (717),

glucagon (70), and possibly vasopressin (941). The hypolipidemic drug, nafenopin, increases liver weight (382) and promotes a profound choleresis in rats (732) although the mechanism for choleresis is not completely understood. In addition, dihydroxydibutyl ether increases canalicular bile flow without affecting bile acid excretion (215). Administration of non-toxic doses of perhexiline maleate stimulates bile flow and bile acid excretion but inhibits BSP transport maximum (T_m) and its choleretic effect (494). Tienilic acid is choleretic when administered intravenously and does not undergo enterohepatic circulation (736). Bucolome, a non-steroidal, anti-inflammatory drug, produces a pronounced choleresis without increasing bile acid excretion (617, 618). Although 27 μl of bile are excreted per micromole of bucolome, the choleresis may not be due to the osmotic properties of the drug as only small amounts are excreted into bile.

3. Microsomal Enzyme Inducers. Phenobarbital and some other barbiturates enhance bile flow and the biliary clearance of drugs and endogenous metabolites (159, 620, 621, 663, 992). The time course of bile flow enhancement does not correlate with increased liver weight or microsomal enzyme activity, and other enzyme inducers such as 3-methylcholanthrene fail to stimulate bile production (619, 640). Phenobarbital apparently stimulates bile acid-independent flow in the rat (102, 622, 900) and rhesus monkey (962). This increase in bile acid-independent flow might be mediated through an increase in Na^+-K^+-ATPase (968, 1091). Other microsomal enzyme inducers that are choleretic include carbutamide (1198), diazepam (459), pregnenolone-16α-carbonitrile (PCN), and spironolactone (1110, 1300). The enzyme inducer and hypolipidemic agent clofibrate stimulates bile acid-independent flow and decreases biliary cholesterol excretion (697).

B. Cholestasis

Cholestasis is bile flow stagnation which is usually accompanied by increased levels of biliary substances in blood. Common bile duct stones, sclerosing cholangitis, or cancer of the biliary tree or the pancreas can obstruct bile flow and produce extrahepatic cholestasis. Intralobular obstruction, which occurs during cirrhosis or inflammatory processes, can also cause cholestasis (244). In contrast, drug-induced "intrahepatic cholestasis" is apparently due to biochemical interference with cellular function (1298). This term emphasizes functional derangement of the hepatocanalicular bile secretory system and attempts to differentiate it from other mechanisms that could account for accumulation of biliary constituents in plasma and clinical jaundice. Intrahepatic cholestasis has been reviewed extensively (85, 101, 384, 555, 927, 931, 932, 972, 1028, 1054, 1298).

Our present understanding of the pathogenic mechanisms involved in chemical-induced cholestasis is incomplete. Cholestatic lesions, which are often morphologically and functionally similar to those observed clinically, can be induced by chemicals in laboratory animals. However, no experimental model of cholestasis has been successfully developed which duplicates all the manifestations observed in man. Investigations on experimental intrahepatic cholestasis suggest that several different functional alterations may be important. Targets of cholestatic chemicals may be the lipid phase of several cell structures: the sinusoidal and/or canalicular membranes, the endoplasmic reticulum, and the mitochondria. Interactions with lipids or proteins within these membranes can impair cellular functions such as the activity of carrier proteins or microsomal enzymes and the intracellular energy supply. Other targets could be cytoplasmic binding proteins and possibly the microfilaments. Interference with other regulatory processes in the cell may also be important. However, the primary event of drug-induced intrahepatic cholestasis is unknown (932, 1054).

Several chemicals that have been extensively studied will be discussed to facilitate our understanding of bile formation and biliary excretion. A more comprehensive listing of cholestatic agents may be obtained from several reviews (669, 905, 928, 931, 1297, 1298).

1. Endogenous Compounds. a. BILE ACIDS. The toxic effects of the monohydroxy bile salt, lithocholate, have been known since Holsti described a ductular cell reaction in rabbits fed desiccated hog bile (503, 504). Later Javitt (554) reported rapid onset of cholestasis in rats after intravenous infusion of taurolithocholic acid. One hypothesis for this toxic response stated that aqueous solubility of sodium salts of lithocholate and its conjugates is lower than that of potassium salts (1099). Secretion of the bile acid from a high K^+/low Na^+ intracellular environment to a high Na^+/low K^+ biliary environment could result in intracanalicular precipitation of sodium taurolithocholate (557, 1099). Abolition of cholestasis by simultaneous infusion of primary bile acids is consistent with this hypothesis (557, 944). The more soluble 3-α-sulfates of tauro- and glycolithocholate are less potent cholestatic agents (346), a response that does not result from a reduced hepatic clearance or biliary excretion of these metabolites (740). Additional studies support the notion that formation of insoluble salts in the hepatocyte or the canalicular lumen may initiate hepatic injury and cholestasis (163). Administration of di- and trihydroxy bile acids prevents or reverses lithocholate-induced cholestasis (576, 718).

More recent studies indicate lithocholic acid directly affects the structure, composition, and function of the canalicular membrane (575–577, 718, 813). Na^+-K^+-ATPase activity is decreased in hepatocyte plasma membranes isolated from rats with reduced bile flow after treatment with taurolithocholate (969). Cholestasis induced by monohydroxy bile acids partially results from inhibition of the ATPase which may be due to loss of

enzyme or decreased membrane fluidity. Significant quantities of free cholesterol are released into the canaliculi from its limiting membrane within minutes of an intravenous injection of taurolithocholate (122). This drastic change in membrane composition could modify active and passive transport properties of the hepatocytes and induce cholestasis. Recent preliminary data indicate that inhibitors of protein synthesis apparently block the cholestatic response to lithocholic acid, suggesting that the microsomes may be potentially involved in mediating the cholestasis (1293). Studies in rats with bile fistulas indicate that taurolithocholate-sulfate has little effect on bile flow; lithocholate-sulfate depresses bile flow by 20% while glycolithocholate-sulfate reduces bile flow by 60% in a dose-dependent manner (1292). Lithocholate-sulfate, mainly excreted as the taurine conjugate, appears in bile soon after administration and does not produce morphological changes as evaluated by electron microscopy. In contrast, glycolithocholate sulfate produced membrane-bound cytoplasmic vacuoles as early as 10 min after injection while appearance of the bile acid in bile was delayed. Thus, sulfated glycolithocholic acid is cholestatic in rats by a mechanism apparently different from that of lithocholic acid (1292).

The transmembrane potential of the hepatocyte, an indicator of the structural integrity of the plasmalemma, is altered following administration of bile acid (874). Hyperpolarization was observed after treatment with taurolithocholate at doses that decrease bile flow and hepatobiliary permeability (874). In contrast, taurocholate produces slight depolarization and increases in bile flow and permeability. However, lack of understanding of the mechanisms which maintain the resting membrane potential in hepatocytes makes accurate interpretation of these data difficult.

Intrabiliary pressure generated during retrograde intrabiliary infusion of saline was increased while bile flow decreased after intravenous infusion of taurolithocholate (552). Simultaneous infusion of taurocholate or glycocholate with taurolithocholate prevented the rise in intrabiliary pressure and cholestasis, while the choleretic bile acids decreased intrabiliary pressure. These changes in intrabiliary pressure were likely the result, and not the cause, of more fundamental alterations of bile formation and hepatocyte morphology.

Bile acids other than lithocholic acid and its conjugates are also cholestatic. Drew and Priestly (264) ranked the cholestatic potency of three bile acids as taurodeoxycholate > taurochenodeoxycholate > taurocholate when infused into rats. Bile acid overload appears to lead directly to cholestasis. Administration of tauroursodeoxycholate prevented taurocholate-induced cholestasis (612). Additional studies indicate the allo-monohydroxy bile acids are cholestatic in rats (1215) and that a) 3-β-hydroxy-5-α-cholanic acid (allo analog) is a more potent cholestatic agent than the 5-β analog; b) sulfation does not reduce or prevent depression of bile flow; and c) allo-monohydroxy cholanic acid causes dilatation of canaliculi with partial or total loss of microvilli and formation of pericanalicular diverticuli. A recent report suggests that the potency of dihydrotestosterone glucuronide is greater than the allo bile acids which is greater than taurolithocholate in producing cholestasis (818). The order of potency of bile acids to produce hemolysis (892) is similar to their cholestatic potential. The reproducible, reversible cholestatic response induced in rats by intravenous bile acid administration may be useful in studying the characteristics of intrahepatic cholestasis. However, attempts to modify this response by drugs that produce cholestasis in man (chlorpromazine and erythromycin) do not appear to provide a suitable toxicological approach to prediction of their cholestatic potential (265).

b. MANGANESE-BILIRUBIN. Early studies by Witzleben and colleagues (1274–1277) indicate that acute intravenous administration of manganese sulfate reduces bile flow and the Tm for bilirubin excretion into bile, and produces ultrastructural changes resembling the cholestatic response. Bile flow was further reduced in a dose-dependent manner after injection of bilirubin. In addition, the manganese-induced ultrastructural changes were exacerbated by bilirubin and the cholestatic mechanism was postulated to involve intracanalicular precipitation of a manganese-bilirubin complex. However, when BSP was infused into the animals to prevent the manganese-bilirubin cholestasis, biliary excretion of manganese was significantly increased. Hence, the concentration of manganese in bile may not be a determining factor but the interaction between manganese and bilirubin at the level of the hepatocyte may be more important.

Use of the manganese-bilirubin-induced cholestasis as an experimental tool has been developed (236–238). Combination of low, non-cholestatic doses of manganese and bilirubin produces a rapid and reversible reduction in bile flow if the substances are injected in proper sequence and time interval (634), i.e. manganese first followed by bilirubin 15 minutes later. Recently, de-Lamirande and Plaa (239) demonstrated that 1,3-butanediol, a potentiator of haloalkane hepatotoxicity (480), exacerbated manganese-bilirubin-, taurolithocholate-, and α-naphthylisothiocyanate-induced cholestasis. Potentiation of manganese-bilirubin cholestasis could occur by enhancement of biotransformation leading to increased bilirubin availability and/or increased susceptibility of cellular constituents to maganese. A recent report notes a marked modification in the amount of bile canalicular membranes obtained by differential centrifugation after manganese-bilirubin. These authors suggest that manganese induces changes in the membrane lipid layer that permits bilirubin incorporation and subsequent cholestasis (240).

2. *Drugs.* a. STEROIDS. Cholestasis induced by ana-

bolic and contraceptive steroids has been observed in humans and laboratory animals (928). In humans, estradiol, estriol, and oral contraceptives provoke a reversible retention of BSP and an increase in plasma alkaline phosphatase activity (679, 683, 861). Estrone produces a 30% reduction of bile flow in female rats during both the basal period and during dehydrocholate-induced choleresis (352). Rats given ethinylestradiol for 5 days develop hepatomegaly and depression of both basal and BSP-stimulated bile flow (492). Estrone causes a 50% decrease in steady-state BSP excretion by affecting its active transport into bile. Similar effects have been observed after ethinylestradiol (446, 683). Estradiol-17β decreased bile flow and the biliary excretion of diphenylhydantoin in perfused rat liver and in vivo (1220). Chronic estrogen administration reduced biliary excretion of BSP, bilirubin, and other organic anions in humans (203, 714, 821) and rats (376, 474, 475).

Anabolic steroids such as methyltestosterone and norethandrolone produce dose-related increases in BSP retention (472, 726, 1205). Norbolethone also impairs clearance of BSP and indocyanine green in isolated perfused rat livers (79) and decreases bile flow in higher concentrations. Furthermore, norethandrolone, estradiol, and progesterone inhibit taurocholate uptake into isolated hepatocytes (1055).

Estrogens inhibit bile flow of both bile acid-dependent (446, 805, 913) and -independent (446, 805) fractions. These effects may result from increased permeability of the biliary tree (352, 913), increased microviscosity of hepatocyte membranes (595, 1091), or a decrease in concentration of Na^+-K^+-ATPase (233, 474, 968), but are not due to an alteration in bile acid carriers (1090).

Recent evidence indicates the D-ring glucuronide conjugate of estradiol is cholestatic in rats (804). In fact, intravenous injection of several steroids conjugated with glucuronic acid on the D-ring, but not the A-ring, induces an immediate, dose-related, reversible cholestasis. Thus the cholestatic effect of several steroids might be due to the glucuronide conjugate (805).

Administration of phenobarbital, which increases the bile acid-independent fraction of bile flow, reverses the ethinylestradiol-induced cholestasis (440). Furthermore, clearance of infused taurocholate was reduced in ethinylestradiol-treated rats and was not reversed after phenobarbital pretreatment (446, 1090). Triton WR-1339, a nonionic detergent, has been shown to return the decreased membrane fluidity produced by ethinylestradiol toward normal and reestablish basal bile flow and bile acid excretion (1090). However, Hoenig (492) has recently been unable to reproduce these protective effects of Triton WR 1339 on ethinylestradiol-induced changes. Coadministration of S-adenosylmethionine has also been shown to reverse the cholestasis produced by ethinylestradiol, possibly by enhancing the biliary excretion of its methylated metabolites (1143, 1144).

Although the results in laboratory animals may be indicative of cholestasis, no demonstration of fully developed intrahepatic lesions has been made. However, signs very similar to those of intrahepatic cholestasis in man have been reported in some strains of mice (DS and C57BL, most sensitive; CBA and C3H, intermediate; and ICR, least sensitive) but not in Sprague-Dawley rats (533). These large species and strain differences in susceptibility to steroid-induced cholestasis may be due to variations in inherent tissue sensitivity or in biotransformation.

b. ERYTHROMYCINS. There are several clinical reports of mild reversible cholestasis associated with use of the lauryl sulfate salt of erythromycin propionate (138, 756). Other derivatives have a lower potential to produce cholestasis (184). Signs of a typical cholestatic reaction include hyperbilirubinemia, elevation of serum aspartate aminotransferase and alkaline phosphatase activities, and fever. An erythromycin-induced cholestatic reaction in experimental animals in vivo has not been demonstrated (928). However, reduction of bile flow in the isolated rat liver has been observed after treatment with erythromycin propionate and its lauryl sulfate salt (598). Inability to demonstrate cholestasis in laboratory animals may be related to species variation. Biliary excretion of erythromycin is the major route of elimination in the rat, but the importance of this route in man is equivocal (830, 831). The most cytotoxic erythromycin in cultured Chang cells (hepatocytes) was the propionate and relative cytotoxicity correlated with surfactant properties (272). A similar relationship between surfactant properties and cytotoxicity in in vitro preparations has been noted for bile acids, phenothiazines, and the laxative dioctylsulfosuccinate (275).

c. PHENOTHIAZINES. Intravenous injection of chlorpromazine reduces bile flow in dogs which is accompanied by an increase in bilirubin concentration (1077) and an increase in intrabiliary pressure (1126). Similar results were observed in rats (673). Whether chlorpromazine-induced neurohumoral changes could be responsible is unknown (1123). Chlorpromazine decreases bile flow in monkeys (1003, 1149), which may be due to inhibition of Mg^{++}- or Na^+-K^+-ATPases (1023), and depresses the plasma clearance of BSP (291). Chlorprothixene-induced cholestasis is also characterized by a decrease in bile acid-independent flow which depresses the biliary clearance and Tm for BSP (2). Other neuroleptics, *cis*-thiothixene and both *cis* and *trans* isomers of flupenthixol and clopenthixol, cause dose-dependent reductions in bile flow, and elimination of BSP and indocyanine green (3). Decreased anion excretion is not due to an effect on hepatic uptake or BSP conjugation rate. These data indicate depression of bile acid-independent flow by an unknown mechanism.

Hepatotoxicity has been demonstrated in isolated perfused rat liver as a reduction in bile flow and BSP

excretion after addition to the perfusate of chlorpromazine (594, 599, 1000), other phenothiazines (1185), chlordiazepoxide, (5) or chlorprothixene (2). Dose-related leakage of intracellular enzymes from isolated hepatocytes is observed after exposure to phenothiazines (2, 273), thioxanthenes (6), and tricyclic antidepressants (4). Chlorpromazine also inhibits bile acid excretion when added to the perfusate in isolated liver of the rat (1166). Although hepatic perfusion is reduced, the inhibition of taurocholate excretion by chlorpromazine is predominantly due to a generalized effect on the plasma membranes of hepatocytes (1165). In fact, these in vitro results may be manifestations of a direct toxic effect of the surfactant properties of these drugs (274, 1021, 1288, 1289), implying that surfactant interactions could be a major mechanism for production of intrahepatic cholestasis.

3. Other Chemicals. a. α-NAPHTHYLISOTHIOCYANATE (ANIT). A single dose of ANIT produces a dose-dependent cholestasis and hyperbilirubinemia in susceptible species such as rat and mouse (83, 84, 535, 925). In the rat, onset of hyperbilirubinemia occurs between 12 and 24 hours and peaks at 5 days before returning to normal values at about 7 days. The decrease in bile flow is more abrupt in mice, occurring between 16 and 24 hours and lasting about 5 days (263, 535, 746). Hamsters are more resistant and require larger doses to induce the response whereas dogs are completely resistant to the cholestatic effects of acute ANIT administration (535). Even before cessation of bile flow, ANIT produces retention of BSP (84) and bilirubin (991) in plasma by affecting hepatic uptake of the exogenously administered compound. In addition, ANIT increases plasma alanine aminotransferase activity in rats (263) and dogs (535). Concentrations of 5′-nucleotidase (263), BSP, and taurocholate (684) increase in plasma after ANIT administration thus indicating that increased leakage across the tight junctions may contribute to the regurgitation of these substances and enzymes in blood (684). Incorporation of radiolabeled δ-aminolevulinic acid into bilirubin increases after ANIT administration in a dose-related manner (993). This suggests that enhanced bilirubin synthesis may also be involved in drug-induced hyperbilirubinemia. Finally, ANIT causes an impairment of microsomal enzyme activity (150, 263, 432, 929).

Pretreatment of rats with inhibitors of protein and RNA synthesis block ANIT-induced hyperbilirubinemia and cholestasis (536, 1186). A direct effect of these inhibitors on the enzymes involved in ANIT biotransformation is possible (156, 748, 1095) but not completely established. However, these inhibitors do not affect early BSP retention or prolong pentobarbital-sleeping time (537).

Hepatic clearance of exogenously administered bilirubin is reduced in ANIT-treated rats and mice before complete cessation of bile flow occurs (991). Moreover, the maximal rate of bilirubin excretion into bile is significantly diminished. ANIT decreases the uptake of bilirubin into the liver even in mice with bile duct ligation but does not influence bilirubin conjugation. Thus, ANIT appears to have a direct effect on hepatic uptake, storage, and biliary excretion. However, the mechanism of the acute action of ANIT is complex and further studies are needed to clarify the causes of cholestasis.

b. CHOLEPHILIC ANIONS. Hepatic transport of cholephilic organic anions has been widely studied to elucidate the mechanisms of bile production, hepatic uptake, and elimination. Indocyanine green, rose bengal, unconjugated BSP, and bromcresol green are cholestatic in rats and mice, and eosine decreases bile flow only in mice when administered at doses above the T_m (425, 428). The cholestatic effects of these anions is greater in mice that have a higher basal bile flow rate (428). Cholephils that have a low biliary T_m tend to be cholestatic while those with a high biliary T_m tend to be choleretic (428). The cholestatic effect appears to be due to accumulation of cholephils in the liver because of their limited rate of excretion. Toxic effects of these organic acids as manifested by a decreased bile flow may be due to inhibition of mitochondrial respiration (25, 149, 425, 428, 604, 705, 706) or Mg^{++}- and Na^+-K^+-ATPases (704, 705, 796, 1043, 1044). Other possible mechanisms for cholestasis are discussed in the review of Plaa and Priestly (928).

c. MISCELLANEOUS. Experimental hypothermia induced by administration of anesthetics to rats decreases bile flow and biliary excretion of bilirubin and BSP (990). Other studies in rats and rabbits indicate that hypothermia markedly reduces bile flow, bile acid excretion, and bile acid-independent flow (757). The last effect is thought to be due to a decrease in Na^+-K^+-ATPase activity.

Cholestasis can be induced by administration of phalloidin to rats (268, 269, 297, 312). A decrease in bile acid secretion and an increase in the bile/plasma ratios of inulin and sucrose are observed. Freeze fracture replicas reveal alterations of the junctional complex that separates the canalicular lumen from the lateral intercellular space. A microfilament-mediated change in junctional permeability might permit efflux of biliary constituents into intercellular space during phalloidin-induced cholestasis. Rats made cholestatic by bile duct ligation survive phalloidin poisoning because uptake of demethylphalloin is depressed 75% after 4 hours of ligation (1228). Bile acids prevent phalloidin toxicity in isolated hepatocytes (366) by inhibition of toxin uptake (916, 918).

Aflatoxin B_1 is rapidly taken up by isolated perfused rat livers and approximately 30% of the dose is excreted into bile in 4 hours. Bile flow decreases after 90 minutes and is completely stopped by 4 hours, indicating complete cholestasis (1193).

The antibiotics, novobiocin and rifampicin, produce jaundice and BSP retention (669, 723, 921), which may

be due to inhibition of hepatic uptake of organic anions or inhibition of UDP-glucuronosyltransferase (41, 703, 1104). Rifampicin reduced the biliary excretion of warfarin by 56% (1284).

The oral hypoglycemic drugs, carbutamide, chlorpropamide, and tolbutamide, produce a very low incidence of hepatic reactions including elevated alkaline phosphatase activity and cholestatic jaundice (709). Endotoxin from *Escherichia coli* decreases bile flow in the isolated perfused liver of the rat (1195) which may be accounted for by a decrease in Na^+-K^+-ATPase (1196). Since the endotoxin also causes impairment of BSP and indocyanine green clearance, circulating endotoxin may contribute to the production of intrahepatic cholestasis observed during bacterial infection (1197). Endotoxin is concentrated in liver because two thirds of an intravenous dose is recovered in the organ 8 hours after administration while about 7% is excreted into bile (767). However, the mechanisms for uptake and secretion remain obscure.

In allergic hepatitis, lymphocytes elaborate macrophage migration inhibitory factor which, when administered via a mesenteric vein in rats, produces a marked reduction in bile flow and bile acid secretion (815). Histological changes resemble those for intrahepatic cholestasis and include dilatation of bile canaliculi and loss of microvilli. This factor is not produced by lymphocytes from normal patients. The mechanism whereby this factor from patients with hepatitis induces cholestasis in rats is not understood.

Recently, the tetradecapeptide hormone, somatostatin, was shown to inhibit basal and food-stimulated biliary secretion in the dog (806). Studies in rats indicate somatostatin decreases bile flow by 30%, bile acid secretion by 35% to 45%, and the bile acid-independent fraction of canalicular bile flow. Endogenous bilirubin excretion is not affected (984). A similar somatostatin-induced decrease in bile flow has been observed in dogs (502). Other natural products that induce cholestasis include icterogenin, 22 β-angeloyloxyoleanolic acid, and sporidesmin (283).

Effects of ethanol on bile formation have been reviewed recently (1147). Acute administration produces an apparent dose-related reduction in bile flow and bile acid secretion in dogs, rats, and humans. The acute response is present even if the animal has been fed alcohol chronically. This cholestastic effect is probably due to inhibition of bile acid-dependent secretion. Biliary excretion of BSP and indocyanine green is decreased by acute ethanol administration. Elimination of propoxyphene (864) and lorazepam (510) on first pass through the liver is decreased during acute ethanol infusions. Low ethanol exposure for 3 days depresses transport of methylfolate into bile (1132). Chronic exposure to ethanol apparently stimulates both bile acid-dependent and -independent fractions of canalicular bile flow. Mechanisms for this effect involve alterations in rates of hepatic bile acid synthesis or degradation, intestinal metabolic pathways, and the enterohepatic circulation.

Although the central theme of this review is biliary excretion, understanding the proposed mechanisms of cholestasis assists our comprehension of bile formation and biliary excretion. Based on the aforementioned discussion, the following mechanisms may be involved in intrahepatic cholestasis: 1) impairment of sinusoidal membrane function of hepatic uptake; 2) interference with intracellular binding and distribution; 3) altered bile acid metabolism; 4) interference with mitochondrial energy supply; 5) morphological changes in canalicular membrane such as loss of microvilli and membrane enzymes; 6) disruption of microtubule and microfilament formation and function; and 7) interference with canalicular bile elaboration (928, 972, 1028, 1054).

C. Cholelithiasis

Cholelithiasis, or gallstone disease, is associated with insolubility of cholesterol since it is the predominant solid constituent of gallstones (88, 1153). Cholesterol is maintained in solution in bile by formation of mixed micelles consisting of bile acids, cholesterol, and phospholipids (162, 843, 1097, 1098, 1100). Solubility of cholesterol depends on the relative concentrations of these three biliary constituents. This relationship can be illustrated by triangular coordinates (fig. 5) which can distinguish bile from patients with cholesterol stones from bile of those without (17). Bile from patients with stones is supersaturated with cholesterol (1102, 1207, 1208) and the predominant components of biliary calculi are cholesterol and insoluble calcium salts (1153).

Lithogenesis results from some metabolic defect in liver and may be due to excessive synthesis and excretion of cholesterol, a relative lack of bile acids, or both (438, 602, 853, 961, 1089, 1207, 1208). Increased synthesis and excretion of cholesterol are the predominant events in obese patients (107). However, in the majority of gallstone-forming patients, diminished secretion of bile acids is a fundamental defect that reduces the total body pool of bile acids (1207, 1208). Currently, the most accepted view is that there is an increased cycling frequency of bile acids which suppresses bile acid synthesis (816, 856, 1071). Enzymatic activities of hepatic β-hydroxy-β-methylglutaryl-CoA reductase are higher, and cholesterol-7-α-hydroxylase lower, in patients with gallstones compared to those without (849). Defective conjugation of bilirubin monoglucuronide could result in an increased proportion of this poorly soluble conjugate in bile which may act as a nucleation site for gallstone formation in humans (281). In addition, the functional integrity of the gallbladder is important in maintaining normal bile composition (930). Micellar binding accounts for 80% of the calcium in hepatic bile but only 50% in gallbladder bile, suggesting that calcium binding in soluble micelles lowers the activity of calcium and hence its liability to precipitate as gallstone nuclei (1267). Administration of

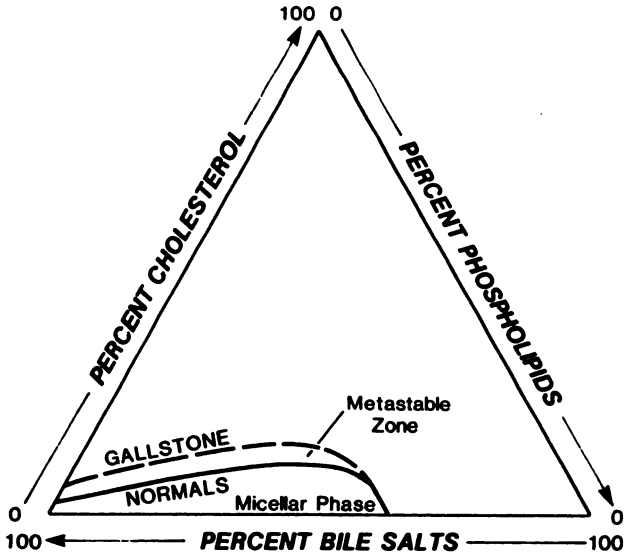

FIG. 5. Triangular coordinates illustrating the relationship of bile acids, cholesterol, and phospholipids. Bile from patients with cholesterol stones can be distinguished from bile of those without.

clofibrate (218) and estrogens (88) increases the lithogenicity of bile and has been associated with a high incidence of cholelithiasis.

Medical treatment of gallstones has been reviewed, and drug therapy is directed toward decreasing the lithogenicity of bile by increasing the bile acid pool (123, 499, 1098). Chronic administration of exogenous bile acids to man (taurocholate, 380; chenodeoxycholate, 64, 220, 229, 540, 550, 775, 1173; ursodeoxycholate, 47, 325, 326, 544, 768, 770, 780, 1020, 1138) decreases cholesterol saturation in bile and induces gallstone dissolution in the majority of patients with radiolucent gallstones. Lithogenicity is reduced decreasing the proportion of cholesterol relative to bile acids and lecithin (13) and perhaps by reducing hydroxymethylglutaryl-CoA reductase (602, 1020). Correlation between cholesterol and bile acid secretion suggests cholesterol transfer across the canalicular membrane is best explained on the basis of incorporation into lecithin-bile acid mixed micelles (461). Secretion of these lipids depends on bile acid secretion (262, 1246, 1250). However, bile acid secretion rate (1224), bile acid structure (390, 496, 1103), and species of animal being studied (91, 1173) can all alter bile lipid composition.

VI. Hepatic Elimination of Xenobiotics

The liver probably developed evolutionarily as a union of a secretory diverticulum of gut endoderm and as a storage organ, and the hepatic portal venous system draining the intestines preceded formation of a proper liver (33). The anatomical position of this organ is particularly advantageous for removing toxicants from the blood after absorption by the gastrointestinal tract. Since blood from the intestine passes through the liver prior to systemic circulation, the liver can theoretically remove a chemical from the portal circulation and decrease or prevent distribution to other parts of the body. The liver is also unique in that chemicals in plasma come in direct contact with the hepatocytes which are not separated from the plasma by vascular tissue as in other organs. Chemicals entering the systemic circulation may be excreted by the kidney or liver or may be biotransformed prior to excretion. Factors determining whether a xenobiotic is eliminated via urine or bile are largely unknown (245, 246, 1114). The relative importance of either route in the excretion of foreign compounds is difficult to ascertain. Studies have often drawn conclusions after quantifying the amount of chemical in urine or feces. In experiments where a chemical was administered orally and later found in feces, the importance of biliary excretion was often minimized by concluding that the fecal fraction resulted from poor absorption and not biliary excretion. Experiments in which the chemical was administered intravenously are generally easier to interpret. However, the importance of biliary excretion may not be recognized if the compound undergoes an enterohepatic circulation and is eventually cleared from the body by the kidneys and may be overestimated if the chemical is excreted across the intestinal wall rather than into bile (1008, 1009). Thus, accurate determination of the role that biliary excretion plays in the elimination of a xenobiotic from the body requires an experimental design which permits analysis of bile for content of the chemical and its metabolites and evaluation of these results in relation to experiments where enterohepatic circulation, plasma disappearance, and urinary and fecal excretion of that compound are also measured.

A. First-Pass Effect

The liver is capable of removing chemicals from blood in one pass through the liver. This phenomenon has been called the "first-pass effect" or presystemic hepatic elimination (385, 386). All chemicals absorbed from the gastrointestinal tract, except for the mouth and rectum, pass through the liver before reaching the general systemic circulation. In addition to extraction and/or biotransformation in the liver, metabolism in intestine and lung and excretion by the lung can also contribute to presystemic elimination. Theoretically, the liver can remove xenobiotics from the blood after absorption from the gastrointestinal tract and prevent their distribution to other parts of the body. However, large interindividual differences in first-pass effect due to variations in hepatic extraction ratios permit different amounts of a chemical to enter the systemic circulation in different patients.

Numerous chemicals are known or expected to undergo a first-pass effect. These include physiological compounds such as bile acids (21, 36, 393, 497, 498, 528, 542, 769, 779, 879, 943), and the pharmacological agents propranolol (1075, 1076), lidocaine (1134), oxyphenbutazone (1258), coumarin (988), sodium chromoglycate (201), propoxyphene (864, 906, 1278), nortriptyline (1209), imipramine (82, 1128), lormetazepam (517), nitroglycerin

(841), methyltestosterone (31), alprenolol (437), morphine (542), nalorphine (543), pentazocine (293), ouabain (526), phenol-3,6-dibromphthalein disulfonate (526), amaranth (526), insulin (1187), diethylstilbestrol (1176), ethinylestradiol (484), Org 6368 (20), prazosin (1011), and manganese chloride (1175). In fact, more than 90% of a low dose of propranolol is cleared from blood after a single pass through the liver (1073). However, presystemic elimination of propranolol appears saturable; no drug is found in the systemic blood when a dose of 0.8 mg/kg is administered to humans or 40 mg/kg to rats. With higher doses, a linear increase in the amount of propranolol in blood is found (1004). Also, the first-pass effect is not different for *l*-propranolol or *dl*-propranolol (545). In addition, hepatic biotransformation of a parent drug may produce metabolites that also undergo presystemic elimination. For example, approximately 90% of monoethylglycine xylidide, a metabolite of lidocaine, is extracted after a single pass through the liver (896), and sequential first-pass elimination of acetaminophen, the metabolite of phenacetin, has been demonstrated (893).

The fractional uptake of insulin in man decreases with increasing insulin dose and is lower during induced hyperglycemia than at fasting (1187). Results suggest hepatic uptake of insulin depends upon plasma glucose concentrations. Clearance from blood of drugs administered systemically with significant first-pass effects is highly dependent upon hepatic blood flow, although presystemic extraction is independent of liver blood flow (850, 851, 894–896). For example, clearance of lidocaine in humans was reduced after administration of propranolol (860). Clearance and metabolism of propranolol and extraction of indocyanine green were decreased by a 25% reduction in hepatic blood flow induced by cimetidine in humans (327). Short-term exposure to polychlorinated biphenyls enhances the intrinsic clearance and first-pass effect of pentobarbital in rats (1133). A pharmacokinetic model to differentiate preabsorptive, gut epithelial, and hepatic first-pass metabolism has been described (205).

Experiments to determine the effect of presystemic elimination on the toxicity of xenobiotics need to be performed. Existence of a first-pass effect would be desirable for a non-therapeutic, toxic compound, preventing its distribution to other parts of the body. However, in cases of decreased hepatic function, the chemical may escape the first-pass effect and produce a greater toxicity. If the toxicant is biotransformed by the liver to a more toxic metabolite that re-enters the blood, an increase in presystemic elimination may increase the toxicity of the chemical (640).

B. Hepatic Clearance

Clearance is a precise physiological measurement of the efficiency of xenobiotic elimination. This concept is closely analogous to those in nephrology and provides a measure which changes linearly with respect to a variation in function. Total systemic clearance is the sum of the efficiency of each route of elimination and does not indicate the site or rate-limiting process. However, for many chemicals, the liver is the major site of elimination and systemic clearance reflects hepatic clearance.

Clearance is the volume of blood from which a drug is completely removed per unit time (1263). At steady state, xenobiotic elimination by the liver can be estimated from the product of hepatic blood flow (Q_H) and the extraction ratio (E_H):

$$Cl_H = Q_H E_H = Q_H\left[\frac{C_a - C_v}{C_a}\right]$$

where E_H is the arterial-venous concentration difference across the liver, C_a is the concentration in mixed portal venous and hepatic arterial blood and C_v is the concentration in hepatic venous blood. Thus, hepatic clearance is a function of liver blood flow and the ability of the liver to extract the xenobiotic as blood perfuses the hepatic sinusoids. To overcome the modifying effect of flow on extraction, total intrinsic clearance may be used to express the maximal ability of the liver to irreversibly remove a chemical by all pathways in the absence of any blood flow limitations. When the hepatocyte plasma membrane is highly permeable to a particular compound, E_H may be expressed in terms of intrinsic clearance, Cl_{INT}, (132, 389, 850) such that:

$$Cl_H = Q_H \cdot \frac{Cl_{INT}}{Q_H + Cl_{INT}}$$

Physiologically, intrinsic clearance is an index of the rate at which a substance crosses the hepatic parenchymal sinusoidal membrane. Intrinsic clearance and liver blood flow are two independent biological variables which influence hepatic clearance and extraction. When intrinsic clearance is low, liver blood flow is adequate to maintain hepatic clearance at the same level as intrinsic clearance. If intrinsic clearance is high, then hepatic blood flow becomes rate-limiting and total hepatic clearance varies in direct proportion to flow. Hepatic clearance is partly flow-dependent for chemicals with intermediate intrinsic values.

Factors that cen alter hepatic blood flow can be physiological, pathological, and/or pharmacological (136, 137, 336, 850, 956, 957, 1261). Physiological factors that decrease flow include upright posture, thermal stress, exercise, (224) and volume depletion (476), while food and supine posture increase hepatic blood flow. Hepatic cirrhosis, cardiovascular collapse, renal hypertension, and congestive heart failure are pathological conditions that decrease hepatic blood flow (1262). Myocardial ischemia produced by occlusion of coronary arteries causes a 60% reduction in hepatic blood flow (377). A diminished sinusoidal perfusion may be responsible for the impaired elimination of propranolol observed in some patients (923) and during experimental cirrhosis (1283). Administration of propranolol, norepinephrine (336), and gen-

eral anesthetics (449, 868, 1068) decrease hepatic blood flow, while glucagon, isoproterenol, and repeated administration of phenobarbital increase flow (867, 868). Normal hepatic perfusion in several species, including man, is 1 ml/min/g of liver (418, 1003). Hepatic blood flow determined under a variety of physiological and pathological conditions or after drug administration is 0.5 to 2.0 ml/min/g of liver (133, 224, 1134).

Blood concentration of a chemical after intravenous and oral administration can be affected by a decrease in hepatic blood flow (1263). For a xenobiotic that has low extraction, systemic clearance and half-life are flow-independent and the blood concentration/time curve is similar over a wide range of hepatic blood flows. However, for a chemical with a high extraction, both clearance and half-life are flow-dependent after either route of administration.Thus, a decrease in hepatic blood flow would increase the half-life of the xenobiotic. Clearance and half-life for chemicals with intermediate extraction ratios are dependent on flow to an extent estimated from knowledge of the extraction ratio.

Alterations of intrinsic clearance can affect the blood concentration versus time curve of a xenobiotic after intravenous and oral administration. The major effect of increasing intrinsic clearance as after microsomal enzyme induction is a proportional increase in the efficiency of hepatic extraction. The area under the concentration/time curve and half-life change in inverse proportion to the change in intrinsic clearance. For a compound with a low intrinsic clearance, a twofold increase in extraction would produce a 50% reduction in half-life. However, systemic availability after oral administration decreases only slightly. In contrast, when intrinsic clearance is high, an increase in extraction produces minimal alteration in clearance or half-life but markedly increases presystemic elimination after oral administration. Peak blood levels are decreased and systemic availability is markedly reduced.

Large changes in the rate of hepatic perfusion may alter regional distribution of blood flow within hepatic lobes and influence the magnitude of bile acid-independent flow without significant changes in oxygen uptake, aminotransferase release, Na^+-K^+-ATPase activity, or evidence of morphological damage (1164).

Many in vivo investigations demonstrating the effect of liver blood flow on systemic clearance and half-life and the dependence of this effect on the original extraction ratio have been reviewed (1261). Studies in isolated perfused rat liver also demonstrate interrelationships of extraction rate, liver blood flow rate, kinetic elimination constants (K_m, V_{max}), and route of administration with respect to the blood concentration versus time curve (133, 597, 1074, 1273). From the hepatic extraction ratio, one can generalize about the disposition of a xenobiotic. In particular, compounds with high or low extraction ratios have definable differences in disposition. If a chemical has a low extraction ratio due to a small intrinsic clearance relative to liver blood flow, then hepatic clearance and elimination half-life will be independent of changes in flow but sensitive to hepatic metabolism. In addition, only a small first-pass effect after oral administration will be observed. In contrast, for a compound with a high extraction ratio, hepatic clearance and half-life will be sensitive to changes in flow and insensitive to alterations in metabolic activity. Such a xenobiotic will exhibit a significant first-pass effect after an oral dose. Chemicals having intermediate extraction ratios have mixed properties, in that clearance is partly dependent on liver blood flow and hepatic metabolism.

C. Hepatic Uptake

Before a solute located in sinusoidal blood can be incorporated into the parenchymal cell, the compound must pass through fenestrations of the sinusoidal epithelia and enter the space of Disse (see fig. 2). Then the solute contacts the microvilli of the plasma membrane and uptake occurs. Besides these structural considerations, the velocity of blood flow is an important determinant of the probability of interaction between solute and microvilli.

The uptake of substances by the liver has been examined by several methods: 1) determination of the rate of removal of a chemical from plasma after administration; 2) study of the partition between plasma and liver cells after infusion for a sufficient time to achieve a steady state; 3) quantification of the hepatic concentration at various times; 4) examination of the ability of the isolated perfused liver to concentrate a chemical from the perfusate; 5) determination of the ability of isolated or cultured hepatocytes to accumulate a chemical from the medium; and 6) measurement of xenobiotic influx into isolated membrane vesicles.

Two methods for the study of hepatic uptake have been discussed recently (401, 666). The in vivo multiple indicator dilution technique (223) has been adapted to study uptake of chemicals at the liver cell surface (401). This process (fig. 6) has been modeled and outflow profiles consist of a throughput component which does not enter the liver (^{51}Cr-labeled red blood cells or albumin labeled with Evans blue dye) and a return component which enters the cell and returns to the plasma space to emerge at the outflow (tritiated water). When the process is concentrative, the throughput component emerges well ahead of the returning component by virtue of the enlarged cellular volume. In a non-concentrative process, the throughput and returning components are not widely separated in time. The uptake of tracer rubidium, like potassium, is a concentrative process while that of tracer glucose is non-concentrative. When intracellular sequestration occurs, the magnitude of the returning component in a tracer experiment is reduced and a decreasing steady state lobular gradient is produced from the periportal to the centrilobular region. Diminution in return-

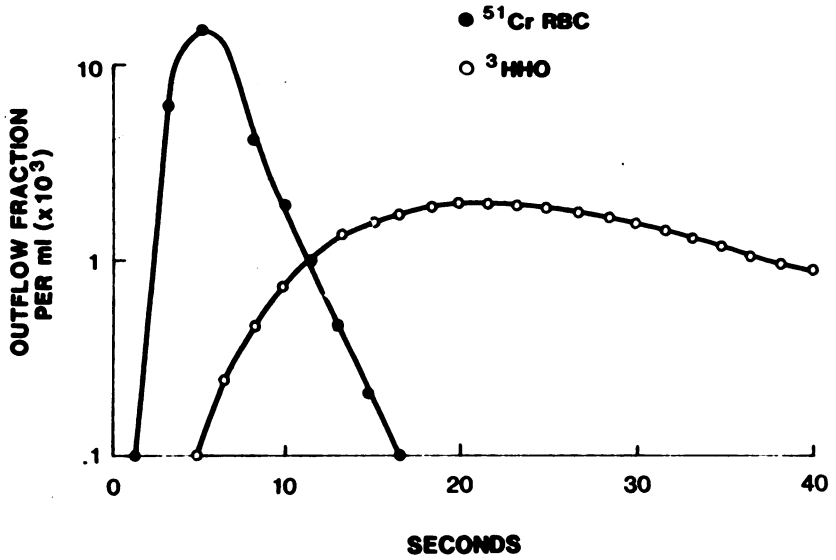

FIG. 6. In vivo multiple indicator dilution technique adapted to study uptake of chemicals at liver cell surface. Outflow profiles are a throughput component which does not enter the liver (^{51}Cr-labeled red blood cells or albumin labeled with Evans blue dye) and a return component which enters the liver cell and returns to the plasma space to emerge at the outflow (tritiated water).

ing components has been observed for galactose, BSP, bilirubin, cholate, taurocholate, and chenodeoxycholate (401, 967). While this technique has been useful, it is very labor intensive, and thus most of the work presently being performed is with isolated hepatocytes.

Suspensions of hepatocytes isolated by the method of Berry and Friend (98) are particularly advantageous for examining the characteristics of the hepatic uptake of chemicals (666, 1053). Isolated hepatocyte suspensions allow rapid, multiple sampling which permits estimation of initial velocities and calculation of kinetic parameters. These cells are useful for studying uptake processes because there is no interference from unspecific binding to plasma proteins, different distributional compartments or hemodynamic factors. However, workers must demonstrate that cell viability is high and maintained throughout the study. Transport characteristics of several classes of compounds have been tabulated recently (1057) which include bile acids (38, 39, 529, 1051), ouabain (284), procainamide ethobromide (285), 3-O-methylglucose, D-fructose, and D-galactose (221, 222), morphine and nalorphine (541), BSP (1058, 1059), BSP-glutathione (1053), insulin (1171), thiamine (755), bilirubin (525), parathion (838), lipoproteins (886, 1199), iron (434, 435), zinc (1121), cadmium (320–322, 1119), estrogens (1060), taurine (464), alanine (687), and other amino acids (175, 292, 328, 571, 721, 722). The majority of these organic compounds appear to be taken up by a carrier-mediated system while lipophilic xenobiotics may pass through the membrane by diffusion (1057). Lidocaine uptake is not carrier-mediated, and binding to intracellular components may account for its accumulation in hepatocytes (176).

Recently, hepatic transport of three xenobiotics, DBSP, *d*-tubocurarine and ouabain, has been evaluated in the rat in vivo, in isolated perfused liver, and in isolated hepatocytes (116). Uptake is similar in vivo and in the perfused liver for all three substrates. However, uptake of DBSP and ouabain into isolated hepatocytes is lower by a factor of 2 to 3, while that of *d*-tubocurarine is similar. Rate of secretion from isolated hepatocytes is identical for DBSP and lower for ouabain and *d*-tubocurarine than that of the in vivo preparation. Results indicate that transport function is well preserved in perfused livers and isolated hepatocytes although, for certain substrates, uptake and/or secretion may be lower in freshly isolated cells of high viability.

1. Bile Acids. Hepatocellular uptake of taurocholic acid appears to be saturable in dogs (393) and perfused rat liver (967). This carrier-mediated transport system is sodium-dependent (114, 967, 1051) and energy-dependent (1051). Uptake of cholate occurs apparently by both simple diffusion and a saturable process and undergoes counter-transport (188) with taurocholate and chenodeoxycholate (39). Transport of cholate appears concentrative in nature but is complicated by conjugation with glycine or taurine and protein binding. The relative potencies of seven bile acids to inhibit cholate or taurocholate uptake suggest several carriers are available for bile acid uptake which may have affinity for more than one bile acid (40). The difference in activation energies between cholate and taurocholate (13.3 and 29 Kcal/mol, respectively) and selective inhibition of taurocholate uptake by ouabain further suggest that multiple carriers are involved in bile acid transport into the hepatocyte. Saturable binding sites for taurocholate and cholate have been demonstrated on rat liver plasma membranes (11). However, uptake is not rate-limiting in transport from blood to bile as the maximal velocity of taurocholate uptake exceeds the secretory T_m by sixfold (967).

Centrilobular hepatocytes have a higher capacity for bile acid uptake than periportal cells (1120). While the K_m of each subpopulation was the same, the V_{max} of the centrilobular enriched fraction was 2.03 nmol/min/mg of protein and that of the periportal-enriched fraction was 1.57.

The hepatic extraction of taurocholic, glycocolic, cholic, deoxycholic, and chenodeoxycholic acids is 80%, 65%, 55%, 55%, and 40%, respectively, indicating that conjugation is more important than the number of hydroxyl groups for bile acids to be removed by the liver (495, 528). Studies determining K_m and V_{max} for bile acid uptake into isolated hepatocytes demonstrate that conjugation with taurine increases the affinity of the bile acid for its transport carrier. In contrast, conjugation with glycine did not affect either V_{max} or K_m. The trihydroxy bile acids have a higher affinity but a lower transporting capacity for the saturable processes than the dihydroxy bile acids. In vivo hepatic extraction appears to be more dependent on the affinity of the bile acids for the carrier system than the capacity at which it can be transported (592).

Uptake of taurocholate into cultured hepatocytes has also been shown to be transported by an energy-dependent, saturable system (1050, 1051) that is sodium-dependent (1036). Similar results were recently observed with isolated rat liver plasma membrane vesicles (538, 1014). Sodium ion-coupled uptake was inhibited by other bile acids and by preloading the vesicles with Na^+. When the electrical potential difference was changed by anion replacement, a more negative potential inside stimulated Na^+-dependent taurocholate transport.

Additional studies indicate that bile acids inhibit the uptake of phallotoxins into isolated hepatocytes (366, 917), suggesting phalloidin and demethylphalloin enter the hepatocyte via the bile acid carrier. Pretreatment with numerous xenobiotics reduces the sensitivity of isolated hepatocytes to phalloidin probably by inhibiting hepatic uptake of the toxin (918).

2. *Bilirubin.* Conflicting evidence exists on the cellular mechanism of bilirubin uptake. Over a wide range of plasma concentrations, hepatic extraction of bilirubin approaches 26% with little change in bile flow or bilirubin conjugation. However, when bolus injections of bilirubin were used to produce higher levels of unconjugated bilirubin in the perfusate than could be attained during constant infusion, the disappearance rate of bilirubin from the perfusate decreases with increasing bilirubin concentrations. These data suggest uptake is a saturable process (119, 903). Other data indicate that deoxycholate inhibits bilirubin clearance from the plasma (118). Moreover, bilirubin uptake can be defined in terms of Michaelis-Menten kinetics and is competitively inhibited by indocyanine green and BSP (1038) but not by taurocholate (903). These data indicate that bilirubin is a likely substrate for a carrier-mediated uptake mechanism. However, other studies report bilirubin clearance depends on binding to both albumin (69) and intracellular binding proteins such as ligandin (728).

In isolated hepatocytes, uptake is extremely rapid and equilibrium between cell and medium is attained within 60 seconds with a 100-fold greater concentration in the hepatocyte (525). The initial velocity of uptake is linear with respect to bilirubin concentration from 12.5 to 200 μM. Pretreatment of cells with various metabolic inhibitors or replacement of sodium ion with choline or lithium ion had no effect on bilirubin uptake. Accumulation was not inhibited by the inclusion of organic acids (BSP or taurocholate) or steroidal compounds (diethylstilbestrol or spironolactone). This study suggests that bilirubin apparently reaches the cytoplasm simply by passive diffusion; however, the high accumulation probably results from association with intracellular constituents.

3. *Exogenous Organic Anions.* Mutant Southdown sheep with normal bile acid uptake are unable to concentrate other organic anions such as BSP, bilirubin, rose bengal, and indocyanine green (217). This evidence of separate carrier systems for organic anionic dyes and bile acids is supported by the observation that taurocholate does not inhibit BSP uptake (1059, 1212). At lower dye concentrations, however, taurocholate can inhibit uptake of BSP (422) and DBSP (1210). A recent study indicates that two systems are involved in BSP uptake by rat hepatocytes and that one carrier is shared with bile acids (707). Taurocholate inhibition reveals a bile-acid-sensitive carrier with a 10-fold higher affinity for BSP than that of the insensitive one, which is probably the Na^+-independent carrier of bile acids (38).

Bilirubin, BSP, and indocyanine green are competitive substrates for a transport system which follows Michaelis-Menten kinetics (400, 1038). Similar results have been obtained with isolated hepatocytes (1058, 1127, 1200). BSP uptake in isolated cells follows Michaelis-Menten kinetics only at low substrate concentrations and is independent of metabolic energy and Na^+ transport. Taurocholate does not affect uptake while indocyanine green inhibits at low concentrations and activates when BSP is greater than 20 μM. Similar findings indicate that DBSP uptake also occurs against an electrochemical gradient and utilizes the sodium ion-dependent carrier (115). Recent work indicates that the hepatic uptake of BSP-glutathione is substantially lower than that of BSP, but both compounds share a common transport mechanism (1052). Hepatocytes with poor viability, as compared to high viability cells, have different kinetic properties for BSP uptake which suggests that the lower BSP clearance observed in patients with impaired liver function may be due to depressed uptake (1059).

Rifamycins, broad-spectrum antibiotics with low toxicity, interfere with the elimination of bilirubin, BSP, and indocyanine green in humans (12) and with hepatic uptake of indocyanine green (899) and bilirubin and BSP

(600) in rats. In addition, hepatic transport of taurocholate is inhibited by rifamycin SV in isolated perfused rat liver (688, 689). These antibiotics inhibit cholate uptake into isolated hepatocytes more than taurocholate uptake and the inhibition appears to be non-competitive (41). Furthermore, hepatocyte uptake of rifamycin is a saturable carrier-mediated process independent of metabolic energy and is not inhibited by BSP. However, BSP uptake is competitively inhibited by rifamycin (703).

Biliary contrast agents are specifically taken up by the liver and are actively secreted into bile. Uptake into rat liver slices is biphasic and consists of a non-saturable, low affinity system and a saturable, high affinity carrier that may be energy dependent. Inhibition of uptake is apparently influenced by the affinity of the agent for plasma albumin (95–97, 741, 749, 750, 819, 822, 823, 1112). Uptake of ethacrynic acid into the isolated rat liver is mediated by a saturable, energy-dependent, and partially Na^+-dependent transport mechanism. Maximal velocity of uptake can be increased by raising extracellular Na^+ concentration (908).

An energy-dependent and saturable system is responsible for the rapid uptake of warfarin but not dicoumarol (1285). A saturable, active transport system has also been shown for both uptake and biliary excretion of orotate which is inhibited by probenecid and *p*-aminohippurate (459). Thus, the hepatic uptake of several exogenous anions appears to occur by a carrier-mediated transport system distinct from that of bile acids, but the number of transport systems and their specificity for uptake of exogenous organic anions requires further examination.

4. Exogenous Organic Cations. Rat liver has an efficient system for uptake and biliary excretion of quaternary (486, 1031) and tertiary (839) ammonium compounds. Uptake is not inhibited by bile acids, BSP, or probenecid (524, 1031). Procainamide ethobromide (PAEB) uptake by rat liver slices is saturable and can be inhibited by omission of sodium ion or addition of the metabolic inhibitors, 2,4-dinitrophenol and iodoacetate (1031). Because liver slices contain both canalicular and sinusoidal spaces, it is impossible with this technique to determine whether this concentration gradient is due to accumulation of PAEB within the hepatocytes or within the bile canaliculi and sinusoidal spaces. PAEB is positively charged regardless of pH and if one assumes a membrane potential of −35 mV (81), a slice/medium concentration ratio greater than 4 would be needed to demonstrate uptake against an electrochemical gradient for a cation if no metabolism or intracellular binding occurred. In the rat, a liver/plasma ratio of unchanged PAEB of 7 has been reported (518).

Recently, isolated hepatocytes have been used to demonstrate that PAEB enters the liver by a carrier-mediated, saturable, and energy-dependent uptake process (285). Initial velocity rates at substrate concentrations from 30 to 400 μM indicate a K_m of 54 μM and V_{max} of 0.13 nmol/min/mg of protein. The process involves active transport because uptake against an electrochemical gradient is evident even after correction for biotransformation and intracellular binding. This system appears to be distinct from those responsible for the accumulation of neutral compounds such as ouabain or organic anions like taurocholate. Whether more than one carrier is responsible for hepatic uptake of organic cations is not known. Transport of numerous tertiary amines may share a similar uptake system with PAEB (839).

5. Neutral Organic Compounds. Farah (323) first suggested that uptake and excretion of ouabain might occur by active transport because accumulation was inhibited in rat liver slices by potassium cyanide. Ouabain uptake is a saturable, energy-dependent process that occurs against a concentration gradient and is not inhibited by organic anions or cations (696). Uptake is inhibited by other neutral steroids such as corticosterone, progesterone, testosterone, and dehydrocholate (695). These early studies suggested that bile acids and ouabain might be transported by the same carrier. However, developmental studies (651) showed that taurocholate transport was near adult levels much earlier than that of ouabain.

Hepatic uptake for ouabain has been studied in detail in isolated hepatocytes (284, 1061). Uptake is saturable, with a K_m of 159 μM and V_{max} of 1.43 nmol/min/mg of protein, and energy dependent as dinitrophenol, potassium cyanide, and rotenone reduced ouabain transport into the hepatocytes. Ouabain uptake is independent of Na^+, which also indicates that its uptake is by a different carrier than that for bile acid transport. Reduction of incubation temperature from 37°C to 27°C greatly decreased uptake velocity, yielding an approximate Q_{10} of 6. Ouabain is transported against a concentration gradient and achieves a cell/medium ratio of about 10 (284). Similar values have been reported in vivo (79, 1016). Several steroidal compounds (six hormones and three cardiac glycosides) inhibit ouabain uptake into isolated hepatocytes, suggesting that they may share the same transport system (284). Recent work with hepatocyte subpopulations indicates ouabain uptake into the centrilobular-enriched population was greater than that into periportal hepatocytes (1020).

The uptake of galactose into isolated hepatocytes appears to be a carrier-mediated diffusion process where the rate of uptake greatly exceeds that of biotransformation (80, 1020). This system is probably different than that which transports ouabain.

A biphasic system has been demonstrated for cortisol uptake into isolated hepatocyes (955) before the steroid becomes bound to intracellular proteins. At low concentrations, uptake occurs by two saturable processes with high and low affinities, respectively, which can be blocked in the presence of the metabolic inhibitors 2,4-dinitrophenol or potassium cyanide. At high concentra-

tions, simple diffusion becomes the major route of cortisol uptake into hepatocytes. Cortisone and corticosterone are competitive inhibitors while dexamethasone, estrone, and testosterone are non-competitive inhibitors of cortisol uptake. Additional studies indicate estrone, estradiol, and testosterone also enter hepatocytes by diffusion and by carrier-mediated transport (954). Similar findings have been observed for the uptake of tri-iodothyronine by isolated (290) and cultured (685, 686) hepatocytes.

6. Metals. A biphasic mechanism is involved in the hepatic uptake of zinc and cadmium. Studies on cadmium transport in isolated perfused rat liver (361, 362, 606) and suspensions of isolated hepatocytes (1121) indicate a simple diffusion phase as well as a carrier-mediated phase that can be inhibited by zinc. Neither phase is affected by administration of metabolic inhibitors. Pretreatment of rats with cadmium chloride, which increases hepatic metallothionein content (288, 1073, 1241, 1242, 1272), increases the rate of the diffusion phase of uptake (1121). This diffusion phase may be related to the intracellular sequestering of cadmium by metallothionein. Cadmium complexes with dithiols (2,3-dimercaptopropanol, dithiothreitol) are rapidly removed from the plasma by Kupffer cells (1096) while either free or non-thiol complexes of cadmium are taken up by parenchymal cells (154).

A similar biphasic response with the first phase showing characteristics of carrier-mediated transport has been observed for the uptake of zinc into 3T3 mouse lymphocytes (1049), isolated rat hepatocytes (1121), and primary cultures of rat liver cells for zinc (320, 321) and cadmium (322).

Ferrous iron is taken up by hepatocyte suspensions by simple diffusion while that of ferric iron is receptor-mediated. Transferrin-bound iron uptake is biphasic: receptor-mediated at low concentrations and by diffusion at higher levels (435). Uptake of ferric iron from iron-transferrin depends on temperature and the transferrin concentration and is inhibited by exposure of hepatocytes to proteases (1291). These data support the role of a surface receptor-mediated uptake component.

D. Macromolecules in Hepatic Uptake

1. Membrane Receptors. a. BILE ACIDS. Specific bile acid binding sites on liver surface membranes have been postulated to represent the initial step in bile acid translocation across the hepatocyte membrane (11). Pretreatment of rats with cycloheximide to block hepatic protein synthesis reduced bile acid transport capacity to 38% of control. Values of liver function tests, bile flow, and histological profiles were all normal. The maximum number of [^{14}C]cholic acid binding sites was reduced 75% 24 hours after cycloheximide, while no effect was observed on the activities of the marker enzymes, Na^+-K^+-ATPase, Mg^{++}-ATPase, or 5′-nucleotidase. The associated alterations in bile acid transport and the maximum number of binding sites after cycloheximide suggests these receptors may be the bile acid carriers (398).

The liver responds to an increased bile acid load by increasing the bile acid excretory maximum (14, 1092, 1235). This substrate-induced effect produces an increase in the number of bile acid receptors which may occur via increased protein synthesis, decreased receptor degradation, or a shifting from a possible intracellular pool to the surface membrane (1092). Whatever the mechanism, the number of putative bile acid carriers can apparently adapt to the taurocholate pool size. Further work is needed to characterize this bile acid receptor both biochemically and functionally.

b. ORGANIC ANIONS. An integral protein from the hepatocyte plasma membrane has been isolated that exhibits a high affinity for BSP (1183). This protein was separated from an acetone powder of a crude preparation of rat liver plasma membrane that was subjected to salt extraction and chromatographed on Sephadex G-100 and then AG-1X8 resin. Based on BSP binding, this isolation procedure gave an approximate 40% yield of BSP binding protein that can bind 100 nmol of BSP per milligram of protein. This receptor is a single protein with an apparent molecular weight of 170,000 and has a dissociation constant for BSP around 4 μM.

An organic anion binding protein has also been isolated from rat liver plasma membrane by affinity chromatography on bilirubin and BSP-agarose (964). It has a molecular weight of approximately 60,000. More recent work indicates that three classes of binding sites are needed to account for the observed BSP binding with capacities of 3.5×10^{-11}, 1.6×10^{-7}, and 5.4×10^{-7} mol/mg of protein (966). BSP-glutathione binding sites had maximal capacities of 5×10^{-11} and 2×10^{-7} mol/mg of protein. BSP-glutathione, indocyanine green, and bilirubin, but not taurocholate, compete with BSP for binding. Demonstration of a saturable binding site with greater affinity for BSP than albumin or ligandin suggests a membrane-bound transport system is responsible for hepatic uptake and biliary excretion of organic anions.

Further studies (1280) indicate isolation of a 5500 dalton protein which has high affinity ($K_a = 0.27\ \mu M^{-1}$) and saturable binding (6.3 nmol/mg of protein) for BSP. This protein is immunologically distinct from ligandin and rat albumin and binds bilirubin ($K_d = 20\ \mu M$).

Thus, three groups have isolated proteins from plasma membranes of liver that bind BSP. Whether the marked differences in molecular weights may be due to differences in polymer formation or to distinct proteins is not known. Also, it is not known whether these BSP binding proteins are the transmembrane carrier(s). While one or all of these proteins may be the putative receptor for organic anions, further studies in animal models with reduced hepatic uptake of organic anions (mutant South-

down sheep and fetal or neonatal animals) may elucidate the relationship of this receptor to hepatic transport.

c. DESIALYLATED GLYCOPROTEINS. Rapid removal of circulating desialylated glycoproteins from blood of mammals occurs exclusively by liver and is mediated by a carbohydrate recognition system present only on hepatocytes (845, 1047). This cell surface receptor recognizes, binds, and internalizes molecules having exposed residues of galactose, N-acetylgalactosamine, and glucose. After internalization via coated pits and coated vesicles, desialylated glycoproteins subsequently appear in a complex network of tubules and uncoated vesicles before reaching the lysosomes where they are degraded (279, 513, 1226, 1227). Studies in isolated hepatocytes indicate only 5% of the receptors (6.7×10^4 receptors/cell) are present on the external surface of the sinusoidal membrane and the rest are in the cytoplasm. Ligand binding to the receptor is time-dependent, saturable, and dissociable ($K_d = 3.4 \times 10^{-8}$ M) (1124). Furthermore, the receptor is apparently stable under conditions where the ligand is being destroyed and hence undergoes recycling such that most receptor molecules are located intracellularly (1160). In spite of the 50% reduction of receptor protein by inclusion of cycloheximide in the medium, metabolism of asialo-orosomucoid was 34 times greater than the amount that could be bound to the receptor (1124), which supports the hypothesis of receptor recycling. Molecular weights for the asialoglycoprotein binding receptor are 104,000 and 109,000 for rat and rabbit, respectively (1125). Infusion of receptor-specific antibody substantially reduces hepatic uptake of asialo-orosomucoid but not that of bilirubin, thereby suggesting that the receptor is essential for clearance of desialylated glycoproteins (1139).

Approximately 70% to 80% of an intravenously administered dose of mannosaminated ribonuclease A dimer and serum albumin is taken up by the endothelial and Kupffer cells of the liver (1270). Since hepatic uptake of non-glycosaminated derivatives was <5%, these proteins are thought to enter hepatocytes via the desialylated glycoprotein receptor-mediated carrier.

d. LIPOPROTEINS. Hepatic uptake of E apoprotein from high density lipoproteins by rat liver is a receptor-mediated saturable process with high affinity for the lipoprotein (1083). Results suggest that the mechanism of uptake is identical for that of chylomicron remnants, and that E apoprotein is the receptor recognition site for chylomicron uptake into liver (164, 165, 173). However, non-parenchymal as well as parenchymal cells are involved in the uptake of cholesterol ester-labeled serum lipoproteins (1199). These data indicate the importance of non-phagocytosing parenchymal cells in the clearance of endogenous compounds.

e. ENDOTOXINS. Receptors for the lipopolysaccharide endotoxin have been detected on the plasma membranes of isolated rabbit hepatocytes (953). Binding to the membrane increases directly with endotoxin concentration between 0.01 to 1.0 mg/ml. Results demonstrate that parenchymal cells are also involved in hepatic clearance of endotoxin.

f. IMMUNOGLOBULINS AND IMMUNE COMPLEXES. Intravenously administered immunological aggregates are taken up by and sequestered in hepatocytes of rabbits and rhesus monkeys (772). Receptors for the Fc portion of immunoglobulin G (IgG) and the third complement component (C3) have been localized on the hepatocyte plasma membrane (368, 505). Small amounts of immune complexes are taken up by non-parenchymal cells (506). The mechanism for the in vivo uptake of foreign compounds such as human IgG by mouse hepatocytes is thought to involve binding to a receptor followed by macropinocytosis (44). Extensive work has characterized the clearance of IgA and IgA antibodies from blood by the liver and subsequent active transport into bile (107, 547, 562, 671, 725, 884). The uptake process appears to be initiated by binding to a receptor, secretory component, which is found on the sinusoidal surface of hepatocytes (347, 883). Receptor-mediated endocytosis is generally associated with coated pits and coated vesicles (318). However, elucidation of the structure of the receptor and the mechanism initiating the formation of vesicles are needed before a complete understanding of the uptake of immunological complexes can be achieved.

g. INSULIN. The initial interaction of ^{125}I-insulin with binding sites on the hepatocyte plasmalemma was demonstrated by electron microscope radioautography (89). Results showed that binding distributed evenly over the sinusoidal and lateral surfaces of the hepatocyte and was notably absent from the canalicular membrane (90). Interaction of hormone with receptor activates pinocytosis and the formed vesicle is transported through the cytoplasm to the Golgi apparatus. Biochemical evidence from studies with isolated hepatocytes indicates that both receptor and insulin are internalized (1172). Light and electron microscopic observations suggest that the pinocytotic process is probably activated by high concentrations of hormone as grains visually appeared close to one pole of the membrane of the macropinocytotic vesicle (89, 90). Photoaffinity-labeling and receptor-specific antibodies have been used to characterize this receptor (548, 1290); however, its biological importance is not completely determined.

h. OTHER CHEMICALS. Additional receptors are involved in uptake of fatty acids (976), hemoglobin-haptoglobin (607), transcobalamin (848), and several hormones such as growth hormone (360), prolactin (121), estradiol (922), etc. A recent review discusses properties of these receptors, transmembrane movement of endogenous and exogenous compounds, and liver plasma membrane biogenesis (318).

2. *Intracellular Proteins.* a. LIGANDIN. In 1969, two proteins designated Y and Z were identified in rat liver

cytosol on the basis of their ability to bind organic anions (348, 728, 981). Y protein, quantitatively the more important protein, has been purified to homogeneity and found to bind various drugs, hormones, and metabolites (540). This protein was termed ligandin and proposed to be an important determinant of organic anion transfer from blood to liver. This hypothesis was based on the following indirect data. 1) A deficiency of ligandin in liver of newborn guinea pigs (728) and monkeys (729) was suggested to account for the observed neonatal unconjugated hyperbilirubinemia. Normalization of hepatic organic anion transport coincided with growth and the appearance of ligandin. 2) A phylogenetic study demonstrated that the elasmobranch bony fish and the gill-breathing mudpuppy have no detectable levels of ligandin, have ony trace amounts of Z protein, and lack selective BSP uptake. All tested lung-breathing amphibians, reptiles, birds, and mammals have appreciable levels of Y and Z proteins and hepatic organic anion uptake (731). In addition, there is an apparent correlation between hepatic BSP uptake and content of soluble binding proteins. Furthermore, ligandin, which is undetectable in gill-breathing tadpoles, becomes detectable after metamorphosis to lung-breathing adult frogs (731). 3) The concentration of ligandin in rat liver increases after administration of phenobarbital, *trans*-stilbene oxide, or butylated hydroxyanisole and is associated with a concurrent enhancement of anion uptake (348, 429, 981). Pregnenolone-16α-carbonitrile induces ligandin and doubles BSP and bilirubin binding (758). However, conflicting data indicate binding to ligandin is not the sole determinant of hepatic organic ion uptake. 1) Mutant Southdown sheep have impaired hepatic uptake of BSP, bilirubin, rose bengal, and indocyanine green yet have normal concentrations of the binding proteins of liver (217). 2) Novobiocin and probenecid interfere with the hepatic uptake mechanism but do not compete with bilirubin and BSP for the binding proteins (728). 3) Little correlation exists between the ability of microsomal enzyme inducers to enhance ligandin levels and the biliary excretion of chemicals (638). 4) Evans blue dye binds appreciably to ligandin in vitro but is not readily taken up by the hepatocytes (728). 5) Although ligandin is barely detectable in the liver of newborn guinea pigs, uptake of BSP on their second day of life is comparable to that observed in adults (1256). 6) Hepatic uptake is reduced in hypophysectomized and thyroidectomized rats although ligandin is increased (981). 7) In vitro, ligandin has a lower affinity for BSP and bilirubin than does albumin, yet these compounds are readily removed from albumin during hepatic uptake (364, 583, 1281).

More recent experiments demonstrate a decrease in bilirubin or DBSP efflux from liver after both phenobarbital-, nafenopin-, or thyroidectomy-induced increases in hepatic ligandin concentration (794, 1281, 1282). The role of ligandin in the transport of organic anions from blood to bile is mainly limited to performing an intracellular binding function (586, 1279). Although no evidence suggests these proteins are responsible for recognition and uptake of organic anions from vascular space, binding to these proteins can reduce anion efflux into plasma.

However, an additional function of ligandin was discovered in 1973 when the BSP that bound to ligandin during gel filtration became conjugated to glutathione (GSH) (589). Subsequently, ligandin was demonstrated to be identical to GSH S-transferase B, one of six distinct GSH transferases in rat liver cytosol (450, 451). Recently it has been demonstrated that BSP binding to ligandin was not affected by the presence of bilirubin or indocyanine green; however, conjugation of BSP was significantly reduced by the latter anion (230). Results suggest the presence of catalytic and non-catalytic binding sites on ligandin. In fact, many organic anions including indocyanine green and bilirubin bind non-covalently to GSH transferases but are not conjugated (103, 584, 585, 601, 739, 1093).

Butylated hydroxyanisole and *trans*-stilbene oxide induce GSH S-transferase, increase hepatic ligandin content, and enhance the biliary excretion of BSP (429). These treatments did not enhance the biliary excretion of DBSP, a phthalein dye that binds to ligandin but is not conjugated with GSH. Thus, ligandin is more important as an enzyme than as a binding protein for the excretion of phthalein dyes. Also, the hepatic accumulation of biliary contrast agents does not correlate with binding to cytosolic proteins (738).

b. METALLOTHIONEIN (MT). MT is a small protein of 6600 daltons that contains approximately 30% cysteine and no cystine residues. MT does not contain any aromatic amino acids or histidine and hence does not absorb ultraviolet light at 280 nm. Absorption at 250 nm does occur and depends on the metal-mercaptide bond. If the metal-free protein, thionein, is prepared by dialyzing MT at a low pH or against ethylenediaminetetraacetic acid (EDTA), this 250 nm absorption disappears (131, 147, 512, 573, 676, 678, 774).

The ability of MT to bind metals is due to the abundance of cysteinyl-free sulfhydryl groups. A stoichiometric relationship of three mercapto residues per metal ion exists. In normal animals, the major metal bound to hepatic MT is zinc (573, 574). Although numerous metals bind MT, their actual binding affinities have not yet been determined.

Concentration of MT in tissues can be increased by administration of metals such as zinc (288, 1117, 1242, 1271) and cadmium (288, 1072, 1242, 1272). In addition, MT can be induced in rat liver by food restriction (139), alkylating agents (677), stresses such as heat, cold, strenuous exercise, etc. (865), and bacterial infection (1108). MT concentration in the liver of hamsters was increased 40% to 80% by hydrocortisone and dexamethasone, and 700% and 2000% by zinc and cadmium, respectively

(655). Data suggest that stress-induced increases in MT concentration could be mediated by adrenal corticosteroids. MT induction by metals is probably not mediated via these steroid hormones since even very large doses do not induce MT to the same order of magnitude as these metals (655).

The physiological function of MT is not known but probably is important in the homeostasis of essential trace elements, such as zinc and possibly copper (131, 315, 656, 668, 778, 985, 986). The function most widely studied is the ability of MT to sequester metals and reduce their toxicity (605, 855, 1241, 1242) by binding metals. MT may increase their uptake into liver in a similar manner to that originally proposed for ligandin for the uptake of organic anions. Indirect support for this hypothesis is available from several studies. A large plasma to liver concentration ratio of about 30 for lead (665) may be due to its binding to MT. The major concentration gradient for copper is also from plasma to liver and appears to be bound intracellularly to a large nondialyzable or nondiffusable protein (628, 1169). The dominant concentration gradient for mercury and methylmercury is also from plasma to liver (639). Since these metals both bind to cytoplasmic MT and concentrate in liver, MT could facilitate hepatic uptake by sequestering the free metal upon entering the liver. However, pretreatment of rats with cadmium to induce MT does not enhance the net uptake of cadmium, lead, arsenic, manganese, copper, mercury, or zinc (649). Induction of MT decreases the biliary excretion of cadmium over 90%, excretion of copper, mercury, zinc, and silver about 60%, and that of lead 20% (179, 193, 649). MT has relatively little effect on the biliary excretion of arsenic, manganese, and methylmercury. These results suggest MT does not influence the plasma disappearance of metals but does cause intracellular sequestration and decreases their excretion into bile.

E. Biliary Excretion

1. Classification of Chemicals Excreted into Bile. Compounds undergoing biliary excretion may be categorized into three classes based on their bile to plasma concentration ratios (135, 137). Class A substances have a ratio of approximately 1.0 and include Na^+, K^+, Cl^-, and glucose. Class B compounds have a bile to plasma ratio usually between 10 and 1000. Examples are the bile acids, bilirubin, BSP and other dyes, and numerous xenobiotics. Class C substances have ratios less than 1.0 and include cholesterol, phospholipids, sucrose, albumin, and other macromolecules.

Most xenobiotics for which biliary excretion is an important route of elimination are class B compounds. Most of the remainder of the review will be concerned with class B compounds except for the next few paragraphs where the biliary excretion of class A and C compounds will be discussed.

Little is known about the mechanism by which compounds of class A are excreted into bile. The distribution of cations in bile is similar to that in plasma as Na^+ ion dominates. Passage of sodium into bile may result from a passive response to actively secreted organic anions, predominantly bile acids, or the formation of the bile acid-independent fraction by active sodium ion transport. Potassium ion appears to reach bile only by passive diffusion (752) with two components: a rapid one compatible with the interstitial paracellular shunt and a slower part which may represent transcellular K^+ movement (409). Chloride ion concentration in bile is influenced by bile acid secretion (74). Species with high bile acid secretion rates such as dogs (1253), rabbits (1026), and man (938) have low biliary chloride concentrations. Bicarbonate ion excretion is influenced by several gastrointestinal hormones and neural stimuli, and a postulated canalicular bicarbonate pump (465) may be partly responsible for elaboration of the bile acid-independent fraction of canalicular bile.

Several lipid-insoluble saccharides are excreted in bile at a concentration similar to or less than that in plasma. In the rat, the bile to plasma ratios of inulin, sucrose, and mannitol are 0.1, 0.2, and 1.1, respectively, which suggests a possible relationship between biliary excretion and molecular size (1030). Biliary lipids are also present in bile at concentrations lower than in plasma, but the origin of these phospholipids and cholesterol is not clear. The role of microtubules and vesicular transport in the biliary excretion of lipids is not known with certainty (1130). However, the canalicular membrane is devoid of the enzymes required for de novo synthesis of lecithin (420). Since microtubule inhibitors decrease lipid excretion into bile and since the biosynthetic enzymes are present in the smooth endoplasmic reticulum, the microtubular network appears responsible for translocation of the lipids from their site of synthesis to the canalicular membrane for excretion (419). Whether biliary lipoproteins analogous to those present in plasma are involved in biliary lipid excretion is still controversial (773, 1040).

The origin of cholesterol in bile is unclear. The importance of phospholipids and bile salts in maintaining cholesterol solubility is discussed earlier in the section on cholelithiasis. The rate of excretion of biliary cholesterol appears independent of the rate of cholesterol synthesis, the level of hepatic cholesterol ester pool, and the amount of cholesterol absorbed from the diet (1190, 1191). In the rat, biliary cholesterol is derived from three sources: 70% from plasma cholesterol, 20% newly synthesized, and 10% from an unidentified hepatic microsomal subpool (420, 753, 1048).

Another major driving force of phospholipid and cholesterol excretion into bile is bile acid secretion (420). Interruption of the enterohepatic circulation of bile acids leads to a substantial decline in lipid secretion in man (1040), rhesus monkey (260, 262), dogs (1157), and rats (461), while cholesterol excretion is less affected (1040).

Studies in healthy human volunteers indicate cholesterol and phospholipid outputs are linearly coupled to bile acid secretion before and after endogenous bile acid pool replacement (1022). The rapidity of the changes in cholesterol and phospholipid secretion suggests that secretory coupling of biliary lipids is altered and not biosynthetic or absorptive mechanisms. Administration of the choleretic BSP causes a dose-related decrease in cholesterol and phospholipid secretion but does not affect bile acid excretion in dogs and humans (1070). It is apparent that complex physiological and physicochemical relationships must be understood before a definitive mechanistic model can be elucidated.

Other class C compounds whose excretion is poorly understood include albumin, immunoglobulins, and other macromolecules. Approximately 80% of the protein appearing in bile is derived from serum proteins and the remainder are bile-specific proteins (257, 258). In rat and mouse bile, few extrinsic canalicular enzymes (alkaline phosphatase, 5′-nucleotidase, and leucine naphthylamidase) can be found in bile under normal conditions (316). These are increased during bile acid-induced choleresis, perhaps by detergent action of bile acids (501). Rabbit, rat, and guinea pig have detectable activities of alkaline phosphatase, alkaline phosphodiesterase, leucine naphthylamidase, and lactate dehydrogenase in bile (207, 394). In addition, the intact trypsin-α_2-macroglobulin complex and some degradation products are excreted into bile by rats (414).

Transfer of proteins into bile is thought to occur by bulk movement via micropinocytosis or by selective passage through a sieving mechanism. Amylase and ribonuclease A in the rabbit (1001) and other ^{35}S-labeled pancreatic proteins in the guinea pig (998) are also secreted into bile in significant amounts. Recent studies (977) demonstrate that horseradish peroxidase 1) remains inside membrane-limited compartments with hepatocytes, 2) reaches the pericanalicular cytoplasm via vesicles 100 nm or larger in diameter, and 3) subsequently enters the biliary space by exocytosis. Similar kinetic constants for hepatic uptake and biliary excretion have been determined for four other glycoproteins (1174).

A significant amount of the plasma-membrane-bound enzyme, 5′-nucleotidase, is found in bile (824), suggesting that membrane fragments may break off of the vesicular membrane or the adjacent canalicular membrane during exocytosis. However, the relevance of this mechanism to production of bile or the excretion of xenobiotics is not known. Insulin is another protein that normally is in bile in lower concentrations than those found in plasma (50, 477). Insulin uptake occurs by pinocytosis of receptor-bound hormone followed by intralysosomal degradation (1171).

A technique combining cytochemistry with quantitative autoradiography (564, 977) has demonstrated that within 20 minutes of injection into the portal vein, insulin and/or metabolites appear in bile, while horseradish peroxidase appears later. Rates of decline in appearance in bile are similar with both proteins. Thus, there seems to be a rapid-transport pathway that moves substances from the sinusoidal surface directly into bile and a slower pathway involving lysosomal complexes. Both proteins have a vesicular transport mechanism for secretion into bile.

Recently, vesicular transport has also been demonstrated for dimeric immunoglobulin A (IgA) and an antigenically distinct glycoprotein called secretory component (347, 825–829, 977, 978, 983, 1140). Additional data suggest that secretory component is the sinusoidal membrane receptor for dimeric IgA (883) (see section VI D f). Uptake of IgA has also been studied in cultured hepatocytes of the rat (562). These proteins are encapsulated by endocytosis and, hence, the vesicles contain associated plasma membrane proteins. During fusion with the canalicular membrane, portions of these vesicles can break off and deposit secretory component and 5′-nucleotidase into bile along with vesicular contents (883). Since the glycoprotein is found free in bile, there may be more receptors than IgA molecules (347). Immunoglobulin transport from plasma to bile is very rapid (884). IgA and IgM are concentrated in bile while IgG, albumin, and transferrin are not (235). Endogenous IgA appears to concentrate in bile ducts rather than hepatocytes (235). At present it is unclear how other proteins such as albumin enter bile; however, such a mechanism may be responsible for the appearance of lysosomal enzymes in bile (214). In contrast to most proteins, IgA and haptoglobin are concentrated in bile of rats and rabbits and have bile to plasma concentration ratios greater than 1.0 (483, 725).

2. Biliary Excretion of Cholephils. Brauer's class B compounds have a bile to plasma concentration ratio greater than 1 and are referred to as cholephils. Biliary excretion is most likely to be an important route of excretion for these compounds since they are concentrated in bile. However, for compounds that have long biological half-lives, such as methylmercury, bile can be an important route of excretion even though it is not concentrated in bile (640). Class B compounds are thought to be excreted by active, carrier-mediated transport systems (640, 648, 1029). Classic properties of active transport are: 1) movement of the chemical against a concentration or electrochemical gradient; 2) substrate saturation such that a Tm is exhibited; 3) selectivity of chemical structure; and 4) the system requires expenditure of energy. Although class B substances are considered to be actively transported, these four criteria are rarely, if ever, met. Use of inhibitors such as dinitrophenol, ouabain, and hypothermia to decrease biliary excretion of a test compound has not consistently determined whether a substance is actively transported by the liver. The third criterion is seldom met, but some specific

examples will be discussed later. However, competition between chemicals for biliary excretion is usually less marked compared to active transport systems in kidney and intestine. The first two criteria are most commonly involved to define whether a compound is actively transported (648, 1107).

Transport maxima and high bile to plasma concentration ratios have been demonstrated for numerous compounds, but these are often ambiguous. Since many compounds undergo biotransformation during passage from plasma to bile, T_m's may reflect the rate of metabolism and not excretion. Misinterpretation of bile to plasma ratios can occur if a compound binds to intracellular proteins such as ligandin, intrabiliary proteins, or is sequestered within micelles. It is difficult to determine with certainty that any chemical is actively transported into bile. The strongest evidence available, however, is presence of a higher concentration in bile than in plasma (1029).

Biliary excretion of endogenous and exogenous compounds requires transport into and out of the liver. A bile-to-plasma concentration ratio greater than 1.0 could result from several possible transfer mechanisms. A compound may penetrate the sinusoidal membrane by passive diffusion and enter bile by an active process; the substance could be transported actively into the hepatocyte and simply diffuse across the canalicular membrane; or the chemical could undergo active transport across both the sinusoidal and canalicular membranes. It should be noted that techniques are available for selective investigation of hepatic uptake (into intact liver, isolated perfused liver, isolated hepatocytes, isolated plasma membrane vesicles) but not the excretory transport step. When measuring the biliary excretion of a compound, the overall production of hepatobiliary transport (uptake plus canalicular transport) is quantified. With our present state of knowledge, compounds can be classified into groups according to their overall hepatobiliary transport characteristics without knowing the cellular mechanism of transfer at each site. In spite of these limitations, it is thought that at least five transport systems are involved in excretion of chemicals by the liver. There are transport mechanisms for: 1) organic anions such as BSP, indocyanine green, bilirubin, and glucuronide conjugates; 2) bile acids; 3) organic cations with procainamide ethobromide (PAEB) as the prototype; 4) neutral organic compounds such as ouabain; and 5) metals (32, 644, 648, 970).

a. ORGANIC ANIONS. Most compounds are conjugated before excretion into bile; the most common pathways are conjugation with glutathione and glucuronic acid. Many compounds are excreted into bile at a higher rate after conjugation presumably because it increases molecular weight and polarity and decreases the toxicity of most chemicals.

i. Conjugated with glutathione (GSH). Chemicals are conjugated with the tripeptide GSH by a family of enzymes referred to as GSH S-transferases (549). These GSH derivatives are subsequently cleaved enzymatically to cysteine derivatives that may be acetylated to form the mercapturic acid.

GSH and oxidized glutathione (GSSG) are also found in bile. The concentration of GSH is lower in bile than liver, and GSSG is higher in bile than liver. However, the concentration of GSH is much higher than GSSG in bile. Elimination of GSH and GSSG may be important in regulating hepatic levels of GSH, but the mechanism for its secretion into bile is not known (23, 24, 141, 289, 587, 588).

Sulfobromophtalein (BSP). BSP has been used widely as a measure of hepatic function and is excreted into bile predominantly as the GSH adduct (209). Conjugation with GSH facilitates BSP excretion into bile by producing BSP-GSH which has a higher excretion rate than BSP (71, 340, 423, 1255) and by eliminating the parent compound which is an inhibitor of BSP-GSH excretion (424). However, the rates of excretion of BSP and its metabolites into bile are much slower than their uptake into liver. This accumulation of BSP in liver, referred to as storage (1249, 1252), results from a difference in the rate of uptake into the liver and excretion into bile, not the amount of ligandin (153). However, there is also an appreciable amount of extrahepatic distribution (642). The importance of GSH conjugation on biliary excretion of BSP has been demonstrated by its decreased secretion into bile when GSH levels have been decreased by feeding a protein-free diet (208), by administration of iodomethane (946), or by diethyl maleate (1204) and by inhibiting GSH S-transferase by benziodarone (945) or various organic analogs of mercury, tin, and lead (152).

Recent evidence further emphasizes the importance of GSH conjugation in the biliary excretion of BSP (429). Butylated hydroxyanisole and *trans*-stilbene oxide induce GSH S-transferase, increase hepatic ligandin content, and enhance the biliary excretion of BSP. However, these inducers do not increase the biliary excretion of BSP-GSH. Similar conclusions result from studies in vitamin A-deficient rats (1087).

The T_m for biliary excretion of BSP and its conjugates is around 1.3 mg/min/kg in rats (479, 660, 1255), 1.3 mg/min/kg in rabbits (660), 0.14 mg/min/kg in dogs (71, 660, 878), and 9.5 μmol/min in man (1252) when BSP is administered. Since BSP produces cholestasis at high doses, it is difficult to measure a true T_m (250). Studies in isolated hepatocytes indicate that transport of BSP-GSH into bile is energy dependent and saturable (1056). Maximal velocity of excretion was 60% of that for uptake and 20% of the maximal velocity of conjugation which suggests that excretion may be the rate-limiting step in BSP elimination into bile.

Others. Ethacrynic acid, a potent and effective diuretic, is also excreted into bile after conjugation with

GSH (178, 658). About 60% is excreted into bile within 4 hours of administration. Pretreatment of rats with phenobarbital increases and diethyl maleate decreases the conjugation of ethacrynic acid with GSH, producing similar changes in its biliary excretion (1229). Diethyl maleate, a compound that is used experimentally to lower liver GSH levels, is conjugated with GSH prior to excretion into bile (73).

ii. Conjugated with glucuronic acid. The most common synthetic reaction produces glucuronic acid derivatives of various substrates, which can be either foreign or endogenous compounds such as steroids or bilirubin. The enzymes carrying out these reactions are UDP-glucuronosyltransferases, and the co-substrate is UDP-glucuronic acid. Accumulating evidence supports the hypothesis that there are multiple forms of this transferase, which differ in preferred substrate and inducibility (280, 1233).

Bilirubin. In contrast to BSP, which is excreted predominantly as the GSH conjugate, bilirubin is excreted as several metabolites (335, 691) but the most common are glucuronide conjugates. Excretion of bilirubin into bile occurs after conjugation with either one (bilirubin monoglucuronide, BMG) or two (bilirubin diglucuronide, BDG) molecules of glucuronic acid (210, 399, 1241). BMG formation is catalyzed by the inducible microsomal enzyme UDP-glucuronosyltransferase (280, 590). BDG has been suggested to be produced by a transglucuronidation reaction catalyzed by bilirubin glucuronoside glucuronosyltransferase (183, 186, 187), although other data suggest BDG is formed by the microsomal system (110, 111). Studies on these two enzymes have been reviewed (185, 590, 1041).

In most species, bilirubin exists in bile mainly as the mono- and the diglucuronides. Bilirubin excretion into bile is almost totally dependent upon conjugation as evidenced by the inability of the Gunn rat, which lacks bilirubin UDP-glucuronosyltransferase, to conjugate and excrete bilirubin while having normal T_m for conjugated bilirubin (42). In addition, the amount of BMG in bile is higher and BDG lower in conditions associated with deficient UDP-glucuronosyltransferase activity, e.g. Crigler-Najjar disease, Gilbert's syndrome, and heterozygous Gunn rats (111, 335, 397, 403, 1237). The excretory transport maximum for bilirubin is also species-dependent ranging from 39 μg/min/kg in man (1194) to 610 in rats (991, 1243). These large species variations may relate to differences in hepatic conjugating capacity, such as the activity of bilirubin UDP-glucuronosyltransferase (335, 433). Maximal biliary secretion of bilirubin into bile appears to be very dependent on UDP-glucuronosyltransferase activity (1203). Moreover, depletion of UDP-glucuronic acid in liver by galactosamine or diethyl ether decreases the conjugation and biliary excretion of bilirubin (433).

Bilirubin is not a choleretic. In sheep during a state of maximal bilirubin excretion, bile flow rate and osmolarity are not changed while biliary sodium ion concentration increases (77). Since no change in osmolarity or bile flow occurs with the increased biliary bilirubin concentration, bilirubin may associate with mixed micelles or form molecular aggregates and mask the osmotic activity of the biliary bilirubin.

Others. Many, if not most, compounds excreted into bile are conjugated with glucuronic acid. Examples include the uricosuric agent probenecid (439), the biliary contrast agent iopanoate (211–213), the synthetic steroid, diethylstilbestrol (627), the disinfectant hexachlorophene (379, 653), the anticonvulsant valproic acid (252, 253, 1234, 1236), the dyes phenolphthalein (199), and phenolsulfonphthalein (phenol red) (467), fluorescein dyes (1240), vitamin D_3 (745), and thyroxine (349, 395).

The importance of glucuronidation on the biliary excretion of a number of compounds is emphasized by the alteration in biliary excretion that is observed after an increase or decrease in glucuronidation. Induction of UDP-glucuronosyltransferase by phenobarbital or 3-methylcholanthrene has been shown to enhance the biliary excretion of thyroxine (349), iopanoate (211), diethylstilbestrol (627), hexachlorophene (653), and valproic acid (1236). However, enhancement of the glucuronidation of morphine does not increase its excretion into bile (373, 534, 910). Depression of UDP-glucuronic acid concentrations by galactosamine or diethyl ether has been shown to decrease the glucuronidation and biliary excretion of diethylstilbestrol, valproic acid, phenolphthalein, and iopanoic acid (213, 433, 1236).

iii. Not Biotransformed. Several chemicals are excreted into bile without prior biotransformation. Some of the chemicals have been used diagnostically to determine hepatic excretory function in man similar to that for BSP. These chemicals have been extremely useful in dissecting the effect that physiological, pharmacological, and toxicological factors have on hepatic excretory function.

Indocyanine Green (ICG). ICG is used clinically to measure both cardiac output and hepatic function and is not biotransformed before excretion (181, 521, 1248). Clearance of ICG from plasma, in contrast to BSP, fits a one-compartment open model and its half-life is very dependent on dose (664) in the first 20 minutes after administration. However, at longer times, ICG elimination is non-linear (1141). It is difficult to obtain a T_m for ICG because of its cholestatic properties (507, 508, 664). Removal of ICG from plasma (3.8 μmoles/min/kg) is much faster than its excretion into bile (0.244 μmoles/min/kg) in rats (901, 902). Biliary excretion of ICG and rose bengal depends on bile acid excretion (427).

Rose Bengal. Rose bengal has been used clinically to measure hepatic function and is not biotransformed before excretion (343, 559, 690). It exhibits a rapid and biphasic disappearance from plasma (646). The rates are similar between 0.01 and 10 mg/kg in the rat but slower

at 100 mg/kg. Rose bengal concentrates in liver and appears to be bound to proteins other than ligandin (646). The transport maximum for rose bengal into bile of rats is 100 μg/min/kg (646).

Phenol-3,6-Dibromphthalein Disulfonate (DBSP). DBSP is the dibrominated analog of BSP, is not conjugated before excretion (553), and is handled by the liver in a similar manner to BSP. The disappearance from plasma, storage in liver, and excretion into bile are similar for both dyes in rats, rabbits, and dogs (662). In humans, the plasma disappearance and storage of DBSP is somewhat greater than for BSP but the T_m for excretion is similar (249).

Others. Several other dyes are excreted into bile without being biotransformed. Amaranth (red dye no. 2) (531, 1012, 1018), eosine (1040), bromcresol green (200), chlorothiazide (466), succinylsulfathiazole (809), and tartrazine (100) are pertinent examples. However, more recent evidence indicates amaranth does undergo biotransformation (1012). Further work is needed to ascertain whether any other of these "non-metabolized" chemicals are biotransformed as well.

b. BILE ACIDS. Originally, a common carrier system was postulated for the biliary excretion of all organic acids. Then, Alpert et al. (32) demonstrated that mutant Corriedale sheep were unable to excrete BSP, iopanoic acid, phylloerythrin, conjugated bilirubin, etc. but eliminated bile acids normally via the bile. Although incapable of excreting BSP-GSH, Corridale sheep secrete unconjugated BSP at a lower rate than normal ewes (76). Further support for independent carriers was obtained by the observations that phenobarbital pretreatment enhances the biliary excretion of BSP and DBSP but not taurocholate (620, 663, 900), that indocyanine green has no effect on taurocholate uptake into the isolated perfused rat liver (902), and that nafenopin decreases the biliary excretion of organic acids but not bile acids (790, 791).

Within the hepatocyte, bile acids are largely bound to cytosolic proteins and subcellular organelles with 1% to 10% free in the cytosol (1145, 1146). The rate-limiting step in the excretion of bile acids (393, 398, 970) is their transport across the canalicular membrane which appears to be a saturable process and is characterized by a T_m under steady-state conditions (obtained by stepwise increased infusions of bile acids). Reported T_m values for taurocholate are 14.2 μmol/min/kg in sheep (473), 8.5 μmol/min/kg in dogs (874), and 13 μmol/min/kg in rats (14, 398, 904). Biliary transport is more efficient for conjugated bile acids than unconjugated analogs, and for trihydroxy bile acids than that of dihydroxy bile acids (971).

However, maximal bile acid secretion for individual bile acids also depends on the toxicity of each acid. Recent data obtained in rats indicate the maximal secretion rate decreases as the toxicity of the bile acid increases (462). Maximal excretion of nontoxic tauroursochenodeoxycholate was about 55 μmol/min/kg or 2.5 times higher than that of taurocholate. Similar results have been observed by others (264, 611).

Bile acid transport depends on maintenance of normal membrane structure in that a decrease in fluidity can reduce the transport maximum. Both periportal and centrilobular hepatocytes can transport bile acids and other organic anions (441, 1120); however, the capacity of the centrilobular cells is higher than the periportal cells (1120). Adaptation to selective biliary obstruction and intraduodenal infusion of taurocholate (14) or its repeated oral administration (1092, 1235) is manifested as an increase in taurocholate excretory transport. This is accompanied by stimulated synthesis of bile acid plasma membrane binding protein which can be blocked indirectly by cycloheximide (398) and directly by binding studies (1092). The transport processes for bile acid uptake and secretion are efficient and rapid allowing an effective enterohepatic circulation of bile acids while protecting the peripheral circulation from high bile acid concentrations and removing the need for a major storage protein.

c. ORGANIC CATIONS. Evidence for an active excretory system at the canalicular membrane for organic bases is the reported bile/liver ratios of 10 or more for total PAEB in the rat (518, 792, 835, 1031). Further studies indicate that several organic bases which are excreted into bile inhibit PAEB secretion. Taurocholate, but not dehydrocholate, enhances PAEB elimination into bile, but PAEB does not affect taurocholate excretion (694, 1031). These effects are not due to binding to micelles (1213) or choleresis (694). Isopropamide iodide decreases the liver/plasma ratio for PAEB and its biliary excretion (835). Similar results have been observed for acetyl procainamide ethobromide (acetyl-PAEB) (837) which has saturable uptake and excretory processes (834). Additional studies indicate that retrograde intrabiliary infusion of the fluorescent probe N-[*p*-(2-benzimidazolyl)phenyl] maleimide reduces the biliary concentration of acetyl-PAEB by 50% (836). These data suggest that binding to exposed sulfhydryl groups on the carrier protein can inhibit cation excretion into bile. Comparison of liver/plasma concentration ratios of PAEB and acetyl-PAEB after administration of sulfhydryl reagents intraportally or via intrabiliary infusion indicates that *p*-chloromercuribenzoate and iodoacetamide inhibit hepatic uptake of the cations, N-ethylmaleimide decreases only excretion, and *p*-chloromercury phenyl sulfonic acid inhibits both steps. Thus, these authors suggest that exposed sulfhydryl groups appear to be present on both uptake and excretory transport systems (833).

The structural requirements for transport by the organic cation pathway are a basic amino group on one side of the molecule and one or more nonpolar groups on the other side making the molecule amphipathic (486,

640). Several bis-onium compounds including *d*-tubocurarine and hexafluorenium appear to be actively transported from plasma to bile (787, 788, 792, 793, 796–798). In spite of marked physicochemical differences, thiazinamium and its sulfoxide analog differ slightly in hepatic uptake and biliary excretion (842). A similar mechanism has been determined for the tertiary amine chloroguanide-triazine in vivo (839). However, transport of bisquarternary compounds is decreased by K-strophanthoside while that of PAEB is not (792). This effect is due to depression of uptake by interfering with binding of the bisquaternary compounds to intracellular organelles (788, 793, 798).

d. NEUTRAL ORGANIC CHEMICALS. Two classes of chemicals eliminated via this system are monosaccharides and neutral steroids. Under normal physiological conditions few mono- or oligosaccharides enter bile. Glucose appears in human bile only when the plasma glucose concentration exceeds 350 mg/dl (970). In the rat, glucose is reabsorbed from bile into liver and little is found in bile until the plasma glucose concentration exceeds 280 mg/dl. This can be blocked by phlorizin, a specific inhibitor of glucose transport (447). Glucose reabsorption from the biliary tree has also been demonstrated by using the retrograde intrabiliary injection technique (872). However, localization of this specific transport system which prevents loss of glucose via the bile remains to be established. No sugar is known to be concentrated in bile.

The second class of neutral compounds include the endogenous steroid hormones and cardiac glycosides. The prototype of this class is ouabain. This cardiac glycoside is not biotransformed (219, 696) before its excretion. Ouabain also does not appear to be bound to components of liver homogenates (696) or ligandin in particular (638). The bile/liver concentration ratio 20 minutes after administration is 70 which suggests ouabain may be excreted by an active mechanism (1016). Although ouabain is tightly bound to micelles, taurocholate administration does not affect its biliary excretion and cannot account for the concentrative accumulation of ouabain in bile (1216).

Biliary excretion of endogenous estrogens varies from 20% to 60% depending upon the species (15). Although the mechanism for steroid excretion in humans is not clear, these hormones are conjugated with glucuronic acid, sulfate, or glucosiduronate (698, 1168) and thus might be excreted by the organic anion transport system. However, in rats steroids appear to be excreted by the same pathway as ouabain (412, 696). Digoxin and digitoxin may be excreted by the ouabain pathway; however, since they are glucuronidated before excretion they are probably secreted by the organic acid pathway.

e. METALS. Excretion of heavy metals into bile has been studied systematically only in the past decade and has been reviewed (644). Although many metals are retained in the body for a longer time than most organic compounds, some metals including lead, manganese, mercury, copper, zinc, and cadmium are excreted into bile to a greater extent than into urine.

i. Copper. More work has been conducted on the hepatic disposition of copper than with the other metals because of attempts to characterize abnormal metabolism in patients with Wilson's disease (hepatolenticular degeneration) (1019, 1136). The main route for excretion of copper is via the feces. Rats excrete 20% of an intravenous dose of copper in the feces within 24 hours and only 6% in urine (888). When administered to humans, 40% is found in the stool within 2 weeks and less than 1% in urine (396, 882).

When administered to an animal, copper is rapidly taken up into the liver by a mechanism that does not appear to be saturable (405). Copper can then be excreted into bile (191, 888), stored in liver (890), or integrated into ceruloplasmin and secreted into plasma (890, 891).

The excretion of copper into bile has been shown to increase with increasing dose in the rat up to 1 mg/kg but not at 3 mg/kg (628). This suggests that a transport maximum for copper has been reached, although excretion may be limited by copper toxicity since 3 mg/kg is near the lethal dose in this species. Copper is excreted into bile against a concentration gradient with a bile/plasma ratio of 20. The major concentration gradient for copper is from plasma to liver while the liver to bile gradient is quite small (628).The copper excreted into bile of rats is associated with two different molecular weight substances (194). In humans, binding to a 5000 dalton protein is thought to reduce its enterohepatic circulation (369).

ii. Lead. Lead is removed from the body at a slow rate. When lead was administered intravenously to sheep, only 5% to 8% of the dose was excreted over a 5-day period; 83% of the eliminated metal was found in feces and 17% in urine (112). When lead was similarly administered to rats and excreta collected for 14 days, 50% of the dose was excreted, of which 70% was found in feces and 30% in urine (167). The rate of excretion of lead into feces is highest during the first day after administration and decreases rapidly thereafter (167, 665); over 20% is excreted into the feces within the first 24-hours, 9% within the second 24-hour period, with a rapid decline to minimal amounts thereafter (665). Most of the lead excreted into feces is via bile (112, 190). In humans, urine appears to be a more important route of elimination (596).

An apparent transport maximum for excretion of lead into bile (1.2 μg/min/kg) suggests that lead may be actively transported (665). The bile/plasma concentration gradient of 100 for lead is largely due to the gradient from plasma to liver, which is 30, and partially due to the gradient from liver to bile. However, the large bile/plasma concentration gradient could be due to binding of lead to cellular or biliary components, since lead is

bound to proteins of varying molecular weights in bile (195). Liver proteins have the highest, plasma intermediate, and bile the lowest affinity for lead. This suggests that lead does not passively move from plasma to bile because of a higher affinity for bile than for plasma but rather that excretion most likely is carrier mediated (665).

iii. Manganese. In contrast to most other metals, manganese is rapidly excreted from the body via the gastrointestinal tract with only trace amounts in the urine. Greenberg and colleagues (415, 416) found that 90% of a 1-mg dose injected intraperitoneally into rats was in the feces within 3 days. When mangnese was administered intravenously to rats, over 50% of the dose was in feces within the first 24 hours and 17% within the second 24-hour period (634). About 40% of the manganese is removed by a single pass through the liver which is a very significant first-pass effect (1175). Additional work indicates the biliary excretion of manganese depends partly on lysosomal uptake and release (1154).

There is an overall bile/plasma concentration ratio greater than 150 for manganese. Approximately two thirds of this overall gradient is due to the gradient from plasma to liver, and about one third from liver to bile. The large bile/plasma concentration ratio is difficult to interpret because much of the manganese is not present as the free cation in bile (634, 1180). Tichy and Cikrt (1180) suggested that manganese may be transferred passively from plasma to bile and then undergoes a nonenzymatic complex formation in bile. Later studies indicate the metal is bound to bile pigments (1181). However, plasma and liver contain ligands with a higher affinity for manganese than bile (634). Thus it would appear that manganese is not transferred from plasma to bile by a passive mechanism, but rather by an active one. About 35% of excreted manganese undergoes enterohepatic circulation (191).

iv. Arsenic. Arsenic is slowly eliminated from the body as are most metals. When arsenic trichloride was adminstered intravenously to rats, 13% was excreted the first day and only an additional 7% in the next 6 days. Of that excreted in the first day, 60% was eliminated in urine and 40% in feces (633). The concentration of arsenic is 600-times higher in bile than plasma. The gradients from plasma to liver and from liver to bile are greater than one, the latter usually being the larger ratio. This high concentration of arsenic in bile is not due to a higher affinity of arsenic for macromolecules in bile than in liver because macromolecules in bile have little or no affinity for arsenic whereas the liver does (633). The high bile/plasma concentration ratio suggests that arsenic is excreted into bile by an active transport system, although no transport maximum has been demonstrated.

v. Mercury. The fecal route appears to be more important than the urinary route for excreting inorganic or organic mercurial compounds in rats. No transport maximum for inorganic mercury appears to exist; as the dose of mercuric chloride is increased there is a proportional increase in its excretion into the bile (639). Mercury is the first metal discussed in this review that is not considered a class B compound. Concentration of mercury in liver is slightly higher and that in bile is about one-fourth that in plasma. Mercury is bound to large molecular weight proteins in bile (471) and about 20% undergoes enterohepatic circulation (191). Recent evidence indicates mercury is excreted into bile with GSH but as GSH auto-oxidizes to GSSG, the metal associates with higher molecular weight proteins (63).

The biliary excretion of methylmercury, like mercuric chloride, is not dose-dependent (639, 857). Bile/plasma concentration ratio after methylmercury chloride is about 10 and is due to the higher concentration of methylmercury in liver than plasma (639, 857). The concentration of methylmercury is considerably less in bile than in liver (639). Most of the mercury in bile is bound to proteins and amino acids (857) after it is excreted as methylmercury glutathione (62, 485, 858, 880).

vi. Cadmium. The major route of excretion of cadmium is fecal (148, 170, 196, 234, 659, 863). Biliary excretion is apparently more important than urinary excretion for cadmium intoxication even in long-term exposure to rats and humans (298). The concentration of cadmium in liver is 150 to 800 times higher than in plasma (659). This is most likely due to saturation of cadmium binding to metallothionein at higher doses. The percent of cadmium excreted into bile is related to dose but opposite to that observed for most chemicals secreted into bile; at higher doses a higher percentage is excreted into bile (179, 180, 659). Thus the bile/plasma ratio increases as the dose increases: the bile/plasma ratio is 2.5 at 0.1 mg/kg and 130 at 3.0 mg/kg (659). The concentration of cadmium in bile is actually lower than in liver. Sephadex gel chromatography studies demonstrate that cadmium in bile is not bound to large macromolecules (471, 676) but is excreted as a low molecular weight compound, perhaps complexed with glutathione (180).

vii. Other Metals. The major route of excretion for zinc is fecal with little being excreted into urine (1082, 1122). The main pathway is not via bile but appears to be across the intestinal wall (680, 802, 810, 1201).

The importance of the oxidation state of a metal on its excretion has been demonstrated for tin (481). While bile is not the major route for excretion of any form of tin, it has been shown that divalent tin is excreted into bile while quadravalent tin is not.

About 70% of silver is excreted into bile and 1% in urine within 4 days of administration (652). Its concentration in bile is about 20 times higher than in plasma. Concentration gradient for silver from plasma to liver is about equal to that from liver to bile. No transport maximum is demonstrable.

Beryllium is also excreted into bile, but urine appears to be important (192). Cobalt is also preferentially eliminated via the urine, but the fraction excreted into bile increases with dose (198).

viii. Role of Glutathione in Metal Excretion. Methylmercury, copper, silver, and zinc are excreted into bile via a proposed mechanism where GSH is the carrier molecule (26–28, 880, 963). High concentrations of GSH are found in rat bile (1 to 3 mM) and the metal-GSH stability constants are very high (silver, $K=10^{15}$; methylmercury, $K=10^{15.9}$). Infusion of GSH enhances the biliary excretion of methylmercury (763). Gel filtration studies suggest that the silver ion in bile is predominantly found in a 1:1 complex with GSH and in some polynuclear complexes with GSH or biliary proteins. Pretreatment of rats with either diethyl maleate or selenite, depleters of GSH (511, 967), inhibits the biliary excretion of copper (26), silver (27), methylmercury (29, 30), and zinc (28). Administration of BSP or indocyanine green, which bind to ligandin, decreases the biliary excretion of methylmercury while bilirubin has no effect (764). These data suggest that glutathione conjugation may be important in the biliary excretion of some metals.

VII. Factors Influencing Hepatobiliary Transport

A. Physicochemical Characteristics of Chemicals Excreted into Bile

1. Polarity and Molecular Size. Two physicochemical factors, polarity and molecular weight, can influence the biliary excretion of a compound (1107). Presence of a strongly polar group or potentially ionizable moiety on a molecule augments biliary excretion. This polar group may be part of the parent molecule or acquired by biotransformation. Conjugations with glucuronic acid, sulfate, glutathione, glycine, and taurine are particularly significant in adding polar groups. Such moieties allow a molecule to exist at physiological pH as a water soluble anion. There is no charged center on the cardiac glycosides and no apparent correlation between polarity of the glycosides and biliary excretion in rats, dogs, rabbits (1016), or guinea pigs (777). However, presence of one or more water-soluble sugar residues can compensate for the lack of a charged moiety and facilitate excretion. Many drugs excreted into bile are eliminated in the form of metabolites. In essence, biotransformation (notably conjugation) augments the biliary excretion by introducing a strong polar center into the molecule and by increasing the compound's molecular weight (1107).

Brauer (135) noted that substances which are highly concentrated in bile are usually organic carboxylic acids with molecular weights greater than 300. Sperber (1115) stated that the compounds efficiently secreted by the renal tubules have low molecular weights (200 to 400), whereas chemicals excreted into bile are larger (molecular weight greater than 400). Studies comparing series of monocyclic benzene derivatives (8), bi- and triphenyls (808), and sulfonamides (809) indicate compounds whose molecular weights exceed a threshold of 325 ± 50 are excreted in appreciable quantities into bile. Threshold molecular weights for biliary excretion in the guinea pig, rabbit, and man are 400, 475, and 500, respectively. Excretion occurs mainly via the bile for xenobiotics with molecular weights greater than 850 (487). Above these thresholds, no relationship exists between the extent of biliary excretion and molecular weight (488, 489). Comparison of the excretion of monoquaternary ammonium cations in bile by rat, rabbit, and guinea pig indicate that molecular weight may not be important in organic cation excretion (516).

2. Plasma Protein Binding. Solutes destined for hepatic metabolism and/or excretion commonly bind to albumin in the circulation and hence, have smaller volumes of distribution. Familiar examples include bile acids, bilirubin, sulfobromophthalein, indocyanine green, and many drugs. Although important in transporting chemicals to the liver, albumin does not play an important role in hepatic extraction or biliary elimination (400, 794, 1038, 1281, 1282). Most chemicals excreted into bile are highly bound to plasma proteins. How free solute becomes available to the cell surface, however, is not clear. The conventional view is that spontaneous dissociation of the albumin-ligand complex allows the liver to remove much more solute than is free in the circulation. For many solutes, however, the affinity for albumin and/or the hepatic extraction fraction is so high that it is difficult to believe that spontaneous dissociation is the only mechanism. For example, less than 1% of serum bilirubin is free in the peripheral circulation, but its hepatic extraction is at least an order of magnitude higher.

Forker and colleagues recently reported that perfused rat livers remove taurocholate (357) and rose bengal (358) substantially faster than can be accounted for by the concentration of free bile acid or rose bengal in the perfusate. Both studies demonstrate that increasing the perfusate albumin concentration leads to a reduction in the extraction fraction that is much less than that predicted by equilibrium binding measured in vitro. Thus it appears that liver cells enjoy a special mechanism for enhancing the dissociation of ligands from albumin and that the release mechanism has a limited capacity.

B. Biological Factors Influencing Biliary Excretion of Xenobiotics

1. Species Variation. The amount of an organic chemical or a metal that is excreted in bile varies widely among species. These differences make it difficult to extrapolate results obtained in laboratory animals to predict effects in humans. Species have been classified into three groups based on the percent of an administered dose of a xenobiotic that is excreted into bile (7, 8). In general, the rat, dog, hen, and mouse are good biliary

excretors; the rabbit, guinea pig, and rhesus monkey are relatively poor; and cat and sheep are intermediate. Unfortunately, the significance of these classifications is reduced by a large number of exceptions. For example, rats excrete about 50% of an injected dose of ouabain into bile in 2 hours whereas only 0.5% is excreted by dogs in that time (1016). Chromoglycate is excreted as well by the monkey as the rat (45). Terbutaline is excreted extensively in rats (40% of injected dose) but not in dogs or man (1% to 2% of dose) (852). Comparison of the excretion of phenol red and indocyanine green in four marine species indicates several species variations (949). Indocyanine green was excreted unchanged by all four fish whereas phenol red was eliminated into bile as the glucuronide by dogfish shark and skates and unchanged by hagfish and flounder. A recent study compared the biliary excretion of eight cholephilic anions by mice and rats (428). Male Swiss-Webster mice excreted indocyanine green, rose bengal, DBSP, and eosine at a rate 120% to 460% higher than male Sprague-Dawley rats. Secretion of bromcresol green and BSP-GSH conjugate were similar in the two species, whereas that of amaranth was lower in mice. Depression of bile production by cholestatic organic anions was stronger, and stimulation of bile flow by choleretic acids was weaker in mice than in rats. Differences in biliary bile acid excretion (mouse, 3.62; rat, 1.42 μmol/min/kg), bile flow rate (mouse, 102; rat, 69 μl/min/kg), and liver weight (mouse, 57; rat, 38 g/kg) but not hepatic ligandin concentration (mouse, 132; rat, 214 nmol BSP/g of liver) may explain the differences in organic anion excretion into bile between mice and rats. Until the biliary secretion of cationic and neutral organic compounds is studied, the mouse can only be tentatively classified as a good biliary excretor. In general, rats and mice may be considered to excrete chemicals into bile better than other species.

There is a paucity of data examining biliary excretion in humans due to difficulties in obtaining samples. However, several xenobiotics have been detected in human bile and have been compiled (657, 999). Commonly used drugs concentrated or readily excreted in bile include meperidine (278), ampicillin (144), several cephalosporin analogs (143, 959), erythromycin (174), clindamycin (145), practolol and acibutalol (594), digoxin and digitoxin (672, 1025), adriamycin (987), vincristine (546), indocyanine green and ioglycamide (86, 488), and the psychotropic agents diazepam and lithium (765, 1064, 1170). Conjugates of several steroids such as estradiol, progesterone, corticosterone, and cortisone are also excreted into bile (698, 1107).

There are also species differences in the rate of biliary transport. BSP is readily excreted by rat, rabbit, dog, and man but the T_m for BSP is 5 to 10 times higher in rats and rabbits than in dogs or man (660, 939). This observation may be due to large variations in bile flow rate since biliary BSP concentrations are comparable. Species variation in the biliary excretion of metals (lead, arsenic, manganese) appears to be due to differences in movement of metal from hepatocytes into bile and not from plasma into liver (644). Biliary excretion of cadmium by rabbits is about 0.16 and that of dogs 0.003 times the rate in rats (659), whereas silver is excreted 0.1 to 0.01 times the rate in rats for rabbits and dogs, respectively (652). Rats consistently excrete lead, arsenic, manganese, and methylmercury to a greater extent than rabbits and both species had higher rates than dogs (633, 634, 639, 665). Species differences in biotransformation may also influence biliary excretion. Ethacrynic acid is a strong choleretic in rats (178, 658) but only slightly choleretic (1078) or even cholestatic (311) in rabbits. Since the increased bile flow is due to the osmotic activity of the glutathione conjugate in bile (178, 658), this species difference may be accounted for by a 10-fold greater rate of glutathione conjugation in the rat (431). Diethylstilbestrol-monosulfate is taken up by the liver of the rat, conjugated with glucuronic acid, and excreted into bile (66, 67). The disulfate conjugate is hydrolyzed to the monosulfate before glucuronidation and biliary excretion. In guinea pigs, however, appreciable amounts of diethylstilbestrol monosulfate are either sulfated, glucuronidated, or unchanged before excretion into bile (66, 67). Finally, species differences in hepatic blood flow and bile flow do not appear to correlate with biliary excretion of all chemicals (1107). Thus, there are no steadfast theories as to the mechanism(s) for species variations in biliary excretion. Obviously, further work is necessary before we have a complete understanding of species differences in the complex process involved in biliary excretion.

2. Sex. Differences in biliary excretion between male and female rats exist but do not necessarily relate to documented sex differences in drug metabolism (591, 659). Sex variations in biliary excretion have been noted in rats for indocyanine green and chlorothiazide (466). Tartrazine (100) is secreted metabolically unchanged. Its excretion is more efficient in female rats. However, another study found no difference in the biliary excretion of ouabain, indocyanine green, amaranth, or DBSP (667).

A recent study indicates a sex difference in biliary excretion of 2,4-dinitrotoluene (120). After perfusion with 20 μM dinitrotoluene, male Fischer 344 rats excreted more 2,4-dinitrobenzyl alcohol glucuronide into bile (392 nmol) than female rats (172 nmol). Capacity for metabolism of 2,4-dinitrophenol and for hepatic macromolecular covalent binding were not different between livers from male and female rats. The major difference between the sexes in the disposition of 2,4-dinitrophenol appears to be the greater excretion of the glucuronide into bile by male rats.

Lactating female rats have a higher basal bile flow (80

μl/min/kg) than normal female or male rats (50 μl/min/kg), and both bile acid-dependent and independent fractions of canalicular bile flow are increased (667). The lactating rats tend to excrete indocyanine green to a greater extent than normal rats, but no significant differences in biliary excretion of DBSP, ouabain or amaranth were observed in male and female rats (667).

3. Age. The effects of aging on drug disposition may result from progressive physiological changes in metabolism, excretion, tissue distribution, and blood flow (609, 610, 1200). The plasma clearance of several drugs that require hepatic metabolism is depressed in aged animals and corresponds with decreased activity of hepatic drug metabolizing systems (659). The terminal disposition phase of benzodiazepines in plasma is slightly longer in geriatric patients and depends on volume of distribution (517, 760, 1069).

Decreased biliary excretion of BSP has been observed in older rats (609). Kitani et al. (614) noted a marked difference in the plasma disappearance and biliary excretion of ouabain between young and older rats. They suggested that differences in bile production may be important for the age-related effects. A recent study has examined the pharmacokinetics of ouabain in 2- and 6-month-old rats (527). Plasma ouabain concentrations were significantly higher in the older rats due to a reduction in the apparent volume of distribution and not a decrease in the biliary excretory rate.

BSP retention in plasma increases significantly in humans around 40 years of age (609). Similar results were observed with indocyanine green clearance in healthy geriatric Japanese men (609). Furthermore, studies of antipyrine and indocyanine green clearance in geriatric patients indicate impairment depends not only on the effects of aging on hepatic blood flow and activity of drug metabolizing enzymes but also on environmental factors such as smoking (1283).

More extensive work has evaluated the development of hepatic excretory function. Newborn animals are not miniature adults, either physiologically or in their response to xenobiotics (259, 761, 1085). Possible mechanisms that may account for differences in sensitivity between mature and immature animals include variations in absorption, distribution, biotransformation, excretion, and sensitivity of affected tissues. Biliary excretion is not mature in newborn rats (626), dogs and rabbits (643), and guinea pigs (1256). Indirect evidence indicates newborn humans also have a decreased capacity to excrete foreign compounds into bile (1206).

The decreased excretion of ouabain in newborn rats has been extensively studied and reviewed (650). Results indicate that neonatal rat liver is unable to extract ouabain from plasma which enables ouabain to produce its toxic effects (625). This relative inability of the liver of newborns to remove xenobiotics from blood has been observed for BSP, BSP-GSH, eosine, indocyanine green, and taurocholate (629, 631, 645, 650, 670). The excretory capacity approaches adult levels by 1 month of age and can be stimulated to develop earlier by pretreatment with microsomal enzyme inducers (637, 645). Decreased hepatic excretory function does not appear to relate to the low ligandin levels in the liver of the newborn (638). Ouabain uptake could not be measured in hepatocytes isolated from 12-day-old rats, thus suggesting that a low hepatic uptake capacity is probably the mechanism by which ouabain exhibits greater toxicity in the newborn rat (1118). Thus, a decreased uptake process appears to be responsible for differences in toxicity of ouabain.

Neonatal rats are tolerant to the toxic effects of phalloidin (1296). Decreased sensitivity of the 5-day-old rats is not caused by lack of microfilaments (19). Isolated hepatocytes from newborns exhibit reduced uptake of both bile acids and ^{3}H-demethylphalloin (918, 1296). Since phalloidin is not biotransformed in the liver (950), tolerance is apparently due to decreased uptake of the toxin (1295, 1296).

Depressed uptake in neonatal animals has been observed for other xenobiotics. Cumulative hepatic uptake of bilirubin is low in young guinea pigs and does not achieve adult capacity until 15 days of age (381). Accumulation of indocyanine green in liver slices from newborn guinea pigs is lower than that in slices from adults (522). Moreover, the transport maximum for indocyanine green is one-third the adult level in neonatal guinea pigs (523).

Hepatic uptake of taurocholate in fetal sheep is similar to that in adults. However, adult liver excretes the tracer dose more rapidly than fetal or neonatal liver which indicates that hepatic bile acid transport is not completely mature (1066). Hepatic transport of eosine is lower and phenobarbital could not increase its biliary excretion in 20-day-old rats (338). The ability of neonatal rats to excrete methylmercury into bile develops between 2 and 4 weeks of age and correlates with the capacity of the liver to secrete glutathione (62). Excretory transport may be limited by the available concentration of GSH.

The increased toxicity of colchicine in newborn rats is largely due to immaturity of hepatic excretory function (519, 520). About 68% of colchicine is excreted into bile within 2 hours in rats (520) against a concentration gradient and the liver/bile gradient is larger. Comparison of excretion in 10- and 35-day-old rats indicates higher plasma and liver concentrations and lower biliary excretion rates for colchicine in the immature rats. Results suggest colchicine is more toxic to newborns because of the lower capacity of the liver to concentrate colchicine and excrete it into bile (519).

Excretion of drugs by the liver into bile cannot be studied directly in newborn rats. However, the morphological development of the biliary tract in rats has been described as an indirect estimate of biliary function (248). From days 16 to 19 of fetal age, the canaliculus is

forming and is defined by an intracellular invagination of two adjacent cell membranes into one of the two neighboring hepatocytes. The canalicular lumen dilates during the first 3 days postpartum but then regresses to normal size and fills with microvilli by day 10. However, hepatic excretory function in the rat remains depressed at 10 days of age. If adult-like canalicular structure reflects secretory function, then maturation of excretory function following day 10 must be due to development of uptake and/or conjugation.

4. Fasting. Fasting induces a slight increase in serum bilirubin concentration in normal humans and patients with hemolytic jaundice (78, 331). A much greater absolute rise in serum bilirubin concentration occurs after fasting in patients with Gilbert's syndrome (93, 334) and appears to result from an acquired depression of hepatic bilirubin UDP-glucuronosyltransferase activity (331, 332). A similar increase in plasma bilirubin is observed in ponies under food deprivation (300). Caloric restriction is responsible for diet-induced hyperbilirubinemia but not alterations in dietary components of carbohydrates, protein, or fat (330). Hepatic clearance of bilirubin (300, 608), BSP and indocyanine green (1129), and bile acids (299) is decreased during fasting.

More recent studies indicate that depressed carbohydrate reserves can affect bilirubin conjugation. Fasting produced a 50% inhibition of UDP-glucose dehydrogenase activity resulting in a 43% decrease in hepatic UDPGA concentration in rats (333). Furthermore, nutritional states can alter UDPGA levels which affects the glucuronidation of *p*-nitrophenol in isolated rat liver (973, 974). Short-term fasting (48 hours) can also increase the turnover of hepatic GSH and decrease its concentration in livers from control or acetaminophen-pretreated rats (716). Acute changes in nutrition can markedly affect other factors of metabolism such as xenobiotic transport, oxygen or energy states, NAD or NADP concentrations as well as the major phase I and conjugation pathways (1179).

However, the complete mechanism of fasting hyperbilirubinemia is not totally understood. For example, data obtained in fasting subjects with Gilbert's syndrome suggest there was no modification in bilirubin clearance but rather an increased intrahepatic production of bile pigment (870). These results are at variance with conclusions made by several laboratories (93, 331, 333, 608, 1129). In addition, the plasma disappearance and biliary excretion of BSP, which is not glucuronidated, are also decreased after fasting (1129).

Results of a recent study suggest alterations in uptake account for the diminished clearance of BSP (708). In fasted rats, two distinct carriers for organic anions appear to exist: a high affinity, Na^+-dependent system and a low affinity, Na^+-independent system. Although total BSP binding capacity was not changed, fasting decreased the affinity of the low-affinity component 53% and reduced the capacity of the high affinity site 50%. In addition, a slight depression of hepatic blood flow and/or an increase in BSP efflux may also affect the plasma clearance of BSP. The higher rate of efflux probably results from a fasting-induced decrease in hepatic ligandin concentration (1129). Administration of glucocorticoids increases the hepatic clearance and uptake of bilirubin but does not influence the biliary excretion of the pigment in patients with Gilbert's syndrome (866). Obviously, the effects of fasting on biliary excretion are complex and may affect the uptake and biotransformation of xenobiotics.

5. Pregnancy. The physiological state of pregnancy affects biliary excretory function in several ways: BSP retention is increased while its transport maximum is depressed; the extraction of bilirubin from plasma is impaired and the serum activity of alkaline phosphatase is enhanced (979, 982). Biliary excretion of 12 different estrogenic chemicals (16), progesterone metabolites (699), cholic and chenodeoxycholic acids (700), biliary lipids (980), diphenylhydantoin (1219, 1222), and BSP (982) is depressed in pregnant animals.

In the hamster, pregnancy decreased bile acid-independent flow, hepatic Na^+-K^+-ATPase activity and cholic acid excretion, and increased the concentration of biliary lipids without altering the lithogenic index (980). The decrease in cholic acid excretion accounts for the diminished secretion of total bile acids and part of the decrease in bile flow.

When examined in pregnant rats both in vivo and in the isolated perfused liver, biliary concentration of 5-phenyl-5-*p*-hydroxyphenylhydantoin glucuronide, the primary metabolite of diphenylhydantoin, was decreased and the liver had apparently lost its ability to concentrate the metabolite in bile (1222). Similar effects on diphenylhydantoin metabolism and excretion can be observed in the isolated perfused rat liver and in vivo following administration of estradiol-17β (1220), and the synthetic estrogen, diethylstilbestrol (817).

UDP-glucuronosyltransferase activity toward estrone and estradiol was decreased by 30% in pregnant rats and rabbits (1221) but was more susceptible to induction by 3-methylcholanthrene. Other studies have demonstrated depression of glucuronide conjugation of steroidal and non-steroidal acceptors (840, 1221). Pregnancy and pretreatment with estradiol-17β decreased UDP-glucuronosyltransferase activities toward morphine and estrone by 20% and 50%, respectively, and could be induced by 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) in pregnant rats (142). Moreover, estradiol depressed the biliary excretion of morphine 3-glucuronide but did not affect bile flow (142). In contrast, pregnancy reduced bile flow slightly but did not alter the excretion of morphine. These data indicate the effects of estrogens, as in pregnancy, on xenobiotic metabolism and biliary excretion

vary with the chemical and the dose and duration of estrogen exposure.

C. Pharmacological Factors Influencing Biliary Excretion of Xenobiotics

1. Microsomal Enzyme Inducers. Chemicals that increase the synthesis of various metabolizing enzymes affect the hepatobiliary disposition of xenobiotics. These agents may produce their actions by influencing one or more of the following factors: hepatic blood flow rate, uptake into the hepatocyte, biotransformation and/or intracellular storage, transport into bile, and bile flow rate.

Changes in hepatic blood flow can markedly alter hepatic extraction of chemicals having a high intrinsic clearance (1164, 1263) (see section VI B). Administration of microsomal enzyme inducers increases the efficiency of hepatic extraction (867, 868), and both plasma elimination and half-life of drugs with high extractions depend on hepatic blood flow rate. Alteration of blood flow by phenobarbital was suggested to be the mechanism for the enhanced clearance of indocyanine green (784); increases in blood flow and intrinsic clearance were directly proportional to the increase in liver mass. However, it has recently been demonstrated that indocyanine green does not have high intrinsic clearance in the rat (526) and earlier that phenobarbital does not enhance the plasma disappearance and biliary excretion of indocyanine green (344, 621).

Microsomal enzyme inducers could affect the uptake of xenobiotics into hepatocytes. Phenobarbital, 3-methylcholanthrene, and pregnenolone-16α-carbonitrile (PCN) affect hepatic uptake of ouabain, PAEB, and taurocholate differently (286). Phenobarbital and PCN significantly increase the initial velocity of uptake of ouabain but do not affect that of PAEB or taurocholate (286) or DBSP (789). 3-Methylcholanthrene does not enhance uptake velocities for these three substrates but does produce a significant increase in their steady-state intracellular concentrations (286). Results suggest that 3-methylcholanthrene inhibits the excretory processes for these substrates. PCN enhances ouabain and not taurocholate uptake, which further indicates independent transport systems for bile acids and ouabain. The data suggest that these microsomal enzyme inducers increase the number of carriers for transport into liver.

Many microsomal enzyme inducers increase liver weight, and the mechanism first proposed to explain the increase in bile flow produced by phenobarbital was that it increased liver weight (992). For several reasons this does not appear to be correct. First, biliary flow and liver weight do not increase at the same rate. Biliary flow is significantly elevated 24 hours after one dose and reaches a plateau between 2 and 7 days of administration, whereas liver weight is not significantly elevated after one dose of phenobarbital and tends to increase throughout 7 days of treatment (619). Second, they do not increase to the same extent. While phenobarbital produces about a 50% increase in bile flow, it only increases liver weight 15% to 25% (619). Finally, the abilities of various microsomal enzyme inducers to increase liver weight and bile flow do not seem to be at all related. Large increases in liver weight without increases in bile flow are produced by 3-methylcholanthrene and benzo(a)pyrene (619, 620).

Extensive studies on the effects of barbiturates on biliary excretion have been reviewed (159, 640, 648). Stimulation of bile flow does not correlate with microsomal enzyme induction; the increase in bile flow occurs earlier than the rise in P-450 (158, 184, 339, 341). While cobaltous chloride, an inducer of heme oxygenase, blocks the increase in cytochrome P-450 produced by phenobarbital, it does not prevent the choleresis. The phenobarbital-mediated increase in bile flow is due to an increase in bile salt-independent flow (102, 622), which may be due to stimulation of Na^+-K^+-ATPase (935, 968, 1091). However, the role of Na^+-K^+-ATPase in bile formation is controversial and some authors have not seen an increase after phenobarbital (595).

Once in the hepatocyte, binding to intracellular components can facilitate accumulation of a chemical in the liver cell. The importance of two such proteins, ligandin and metallothionein, was discussed earlier. However, many xenobiotics that are cleared from blood by the liver do not bind to these components. For example, ouabain does not bind to ligandin (638) yet microsomal enzyme inducers enhance its biliary excretion. Also, the amount of ligandin in liver is not related to the increased biliary excretion after microsomal enzyme inducers (638). Stimulation of the enzymatic properties of ligandin (GSH S-transferase) by butylated hydroxyanisole and *trans*-stilbene oxide enhances the biliary excretion of BSP presumably by increasing the rate of conjugation (429). It appears that the ligandin induced by microsomal enzyme inducers is more important as an enzyme than as a binding protein in enhancing the biliary excretion of drugs.

The importance of biotransformation in biliary excretion is well known (733). Most xenobiotics are made more water soluble by phase I and phase II metabolic reactions, and phase II reactions significantly increase the molecular weight of the xenobiotic thereby enhancing its elimination. For example, 3-methylcholanthrene and phenobarbital pretreatments stimulate the rate of excretion into bile of metabolites of N-N-dimethyl-4-aminoazobenzene (DAB). Conversely, mixed-function oxidase inhibitors, SKF 525A and piperonylbutoxide, and agents which deplete GSH , diethyl maleate and iodomethane, decrease biliary excretion. Metabolism appears to be the rate-limiting step in the elimination of DAB (735) although conjugation with GSH is also involved; later studies showed that N-demethylation is the major rate-determining factor (734). Agents that modify biotrans-

formation also affect the biliary excretion of 4′-(9-acridinylamino)methanesulfon-*m*-anisidide (1084), valproic acid (1236), hexachlorophene (653), and many other chemicals. Administration of phenobarbital to children with intrahepatic cholestasis reduces the concentration of bile acids in serum and increases that of bile acid glucuronides in bile (1137).

Administration of phenobarbital, clofibrate, spironolactone, or PCN to male and female rats stimulates the plasma clearance of bilirubin and its biliary excretion (558, 771, 952, 992, 1110, 1300). PCN enhances rat liver UDP-glucuronosyltransferase activity toward bilirubin (1233, 1237). Furthermore, spironolactone induction of UDP-glucuronosyltransferase increases the conjugation of phenolphthalein and *p*-nitrophenol as well as bilirubin (807). These examples further demonstrate the importance of metabolism on the biliary excretion of xenobiotics.

Administration of spironolactone to rats also increases the biliary excretion of several cardiac glycosides (168, 169, 636), indomethacin (647), and various metals (453–455, 616, 641, 654). Specifically, when injected 15 minutes before mercuric chloride, spironolactone stimulates the plasma disappearance and biliary secretion of mercury. This effect of spironolactone is too rapid to be explained by induction of microsomal enzymes. Apparently, the spironolactone metabolite, thioacetic acid, complexes the metal and causes it to distribute throughout the body in similar fashion to organic mercurials with lower plasma and kidney concentrations and higher levels in blood and other tissues (641). The metal is then excreted into bile as a low-molecular weight complex (1182). However, spironolactone does not influence the excretion of all metals similarly. For example, the concentrations of mercury and copper in kidney and plasma were lower after spironolactone and excretion into bile was increased three- and sevenfold. Spironolactone does not alter the distribution or biliary excretion of lead, manganese or arsenic, increases the kidney concentration of cadmium and silver, and decreases the biliary elimination of silver (654).

Microsomal enzyme inducers also stimulate the excretion of several nonmetabolized organic compounds. More than a decade ago phenobarbital was shown to enhance the biliary excretion of BSP, DBSP, amaranth, succinylsulfathiazole, chlorothiazide, and ouabain (620, 1045, 1255). More recently it has been demonstrated that bromcresol green, BSP-GSH (340, 341), eosine, amaranth, and iodoxamic acid (344) are also eliminated more rapidly into the bile of barbiturate-pretreated rats. The biliary excretion of neostigmine and its two metabolites is also stimulated in phenobarbital-treated rats (1111). However, the increase in excretion of the unchanged drug was greater than that of either 3-hydroxyphenyltrimethylammonium or 3-oxyglucuronide (1111). The mechanism for the enhanced excretion is not known but might be due to an increase in amount of carrier protein (286) or to a stimulation in bile flow causing a "wash out" effect (620). Since the inducers do not enhance the biliary excretion of all compounds such as rose bengal (766) and indocyanine green (344, 620), there might be more than one transport system for the excretion of exogenous organic acids.

The mechanism for the increased biliary excretion of drugs after administration of microsomal enzyme inducers is complex. For some chemicals the difference in rate of biotransformation is important, for others bile flow or hepatic blood flow. The most important factor is probably the ability or number of transport carriers to move chemicals into the hepatocyte and into bile. For many xenobiotics, a combination of these factors is needed.

2. *Chlorotoxicants.* As noted earlier, 3-methylcholanthrene is a microsomal enzyme inducer which does not enhance bile flow, hepatic uptake, or biliary excretion and in fact tends to decrease hepatic excretory function (287, 619, 620). In contrast to the barbiturates that induce a family of isozymes that have an absorption spectrum maximum at 450 nm (P-450), 3-methylcholanthrene induces heme proteins with a maximal absorbance of 448 nm (P-448). The chlorotoxicants 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), polychlorinated biphenyls, polybrominated biphenyls, chlorodecone (Kepone), and mirex are similar to 3-methylcholanthrene and decrease hepatic excretory function.

TCDD pretreatment delays the plasma disappearance and biliary excretion of ouabain and indocyanine green (456, 1062, 1063, 1287) but not BSP or DBSP (1287). The polychlorinated biphenyls are generally regarded as microsomal enzyme inducers, but they impair the elimination of digitoxin by apparently decreasing the activity of the enzymes responsible for cleavage of the digitoxose residues (1042). Mirex and Kepone reduce the biliary excretion of imipramine metabolites and phenolphthalein glucuronide, but not of BSP, despite an increase in bile flow (227, 785). Impaired biliary excretion probably results from decreased transfer of metabolites into bile (785).

The detrimental effects of the chlorotoxicants might be due to an effect on ATPases. Both TCDD (915) and mirex depress the activities of Na^+-K^+-ATPase and Mg^{++}-ATPase (225, 226, 242, 786). The TCDD-induced depression of ouabain excretion was masked by pretreating rats with PCN or spironolactone on days 6 to 9 after TCDD injection (914). Even though ouabain transport into bile is normal, the activities of the ATPases remain depressed suggesting that the carrier system for ouabain is separate and distinct from the two ATPases (915). Peterson (909) has suggested that TCDD causes retrodifferentiation to the neonatal state of hepatic gene expression such that TCDD-poisoned and newborn rats exhibit impaired excretion of ouabain. Pretreatment of

adult TCDD-intoxicated (914) and control newborn rats (637) with PCN produces expression of normal adult levels of ouabain uptake and biliary excretion (456).

3. Bile Acids. Intravenous infusions of bile acids can increase the biliary excretion of BSP (106, 128, 313, 355, 422, 426, 678, 989), indocyanine green (1211, 1218), bilirubin (404, 632), DBSP (1211), and rose bengal (422, 766). However, bile acid administration does not enhance the biliary excretion of ouabain or K-strophanthoside (795, 1216), eosine, BSP-GSH (422), ethoxyquin (1094), acetyl-PAEB, or *d*-tubocurarine (1213).

Bile acids probably even have a physiological role in the biliary excretion of bilirubin. For example, it appears that taurocholate is essential for normal exogenous bilirubin excretion in ponies (300). More recent studies indicate infusions of either chenodeoxycholate or taurocholate (8 to 9 μmol/min) increase bilirubin excretion 60% to 80% following 5 hours of biliary diversion where endogenous bile acid excretion equals the amount being synthesized (301). Infusion of dehydrocholate (10.5 μmol/min) after biliary diversion increases bile flow 45% to 60% and excretion of bile acid 35% above the level due to hepatic synthesis. Bilirubin secretion is not changed. These results suggest that bilirubin excretion depends on the micelle-forming capacity of endogenous bile acids.

Cholestyramine-induced bile acid depletion markedly decreases the excretion of indocyanine green, BSP, rose bengal, and bromcresol green (427). Biliary secretion of these anions is stimulated by simultaneous infusion of taurocholate (422). The mechanism by which the bile acids enhance the biliary excretion of xenobiotics is not clear. Since many organic anions bind to biliary micelles (1211, 1218), formation of macromolecular aggregates would decrease the effective canalicular concentration and back diffusion of these dyes and increase their net excretion (1035, 1218, 1232). However, no differences were observed in binding of organic anions to micelles (1211), and non-micelle-forming dehydrocholate also increases excretion of exogenous dyes (94, 1211). Other studies also suggest that complexation with biliary micelles is not the only factor involved. Excretion of diethylstilbestrol was increased during taurocholate or taurodehydrocholate infusions (820). Since diethylstilbestrol monoglucuronide does not form micelles with taurodehydrocholate, micelle formation alone cannot explain the evidence for bile-flow-dependent, carrier-mediated transport of the conjugate into bile. It is possible that bile acids can facilitate anion transport by allosteric interactions with canalicular membrane carriers or causing changes in membrane fluidity. Finally, interference with storage within the hepatocyte may also influence excretion (125, 1211).

This phenomenon to increase the biliary excretion of xenobiotics is not unique for bile acids. Bucolome enhances ouabain excretion (613) and the Tm for indocyanine green but not for BSP (615). Not all compounds that increase canalicular bile flow increase biliary excretion of xenobiotics. For example, theophylline (70), SC-2644 (867), or ethacrynic acid (1210) do not enhance the biliary excretion of BSP and/or DBSP.

However, bile acids can also depress the elimination of some exogenous cholephils. For example, the excretion of amaranth into bile was inhibited by simultaneous injection of lithocholic, chenodeoxycholic, deoxycholic, cholic, and dehydrocholic acids (430). The inhibitory effect of lithocholic acid may be due to toxic actions on mitochondrial respiration (430) or ATPase function (796).

4. Hepatotoxicants. Chemicals that are toxic to liver cells can affect biliary excretion in several ways. Toxicants can affect hepatic blood flow, uptake into the hepatocyte, biotransformation and storage, excretion, and biliary tract permeability.

Acute treatment with carbon tetrachloride markedly decreases the biliary excretion of BSP (661, 947). Furthermore, rats chronically intoxicated with carbon tetrachloride have a delayed plasma clearance and biliary excretion of indocyanine green (530). Intrahepatic metabolism and/or transport into bile of BSP is also impaired after styrene- or styrene oxide-induced liver injury (171, 172).

Biliary excretion of acetaminophen depends on dose and biotransformation (1088) and is reduced in rats anesthetized with diethyl ether (560). This may be due to decreased conjugation with glucuronic acid since diethyl ether depletes hepatic UDP-glucuronic acid concentration (303, 1238, 1239). Pretreatment of rats with galactosamine and borneol, which also deplete UDPGA (1239), reduces the biliary elimination of valproic acid (1236). Excretion of acetaminophen-GSH conjugate may be reduced after toxic doses of acetaminophen due to suppression of hepatic GSH synthesis (716). Perfusion of rat liver with paraquat produces a 70% decrease in hepatic GSH concentration with a concomitant increase in oxidized GSH excretion into bile (414). Chemical-induced loss of microsomal metabolizing systems has been reviewed (241). Thus, numerous data indicate hepatotoxicants can markedly alter xenobiotic metabolism.

Several studies have attempted to demonstrate liver lobule heterogeneity with respect to drug-metabolizing enzymes (324, 551, 957). However, a comprehensive study of the effects of seven hepatotoxicants (allyl alcohol, aflatoxin B_1, ANIT, bromobenzene, carbon tetrachloride, 1,1-dichloroethylene, cadmium chloride) indicates that poisoning seriously affects the microsomal oxidases without significantly influencing the activities of epoxide hydrolase or the glucuronosyl-, acetyl-, sulfo-, and glutathionyltransferases (432). Although mono-oxygenases are unevenly distributed in the hepatic lobule, no reliable information on localization of conjugative enzymes was obtained by determination of enzyme

activity after chemically induced necrosis of a specific region of the hepatic lobule (432). In vivo metabolism of ethanol or aminopyrine was not affected by regio-selective damage by bromobenzene or allyl alcohol (1269).

After exposure to bromobenzene or carbon tetrachloride, centrilobular hepatocytes contributed to the removal of 13% to 18% of a physiological load of taurocholate. The 50% decrease in bile flow after bromobenzene suggests that damage to the centrilobular region produces alterations in bile production and that 13% to 18% of physiological bile acids reach bile via centrilobular hepatocytes (443). Pentachlorophenol and 2,4,6-trichlorophenol inhibit the excretion of BSP into the medium by isolated liver cells (406). Impaired BSP transport may be due to depressed energy production since both phenols uncouple oxidative phosphorylation in hepatocellular mitochondria. Although acute administration of aflatoxin B_1 decreases bile flow (1193), excretion of BSP in bile is not seriously diminished (165). In contrast, taurolithocholate-induced reduction in bile flow significantly decreases the secretion of adriamycin into bile, and the data suggest that the disposition of this chemotherapeutic agent depends on the rate of bile production (1163). A toxic metabolite of ticrynafen reportedly reduces bile flow and BSP excretion, but the mechanism is not known (1299). Administration of an extract of *Amanita phalloides* significantly increases the permeability of the biliary tree as evidenced by the reduction in recoveries of several markers after segmented retrograde intrabiliary injection (372). Thus, exposure to hepatotoxic chemicals can affect bile flow, xenobiotic transport, and biliary tree permeability.

5. Liver Injury. Injury to the liver generally produces deleterious effects on hepatic excretory function. The jaundice following liver injury results from decreased removal of bilirubin from plasma and its excretion into bile. Dye clearance techniques determine the effect of disease or chemical-induced liver injury on the plasma disappearance and biliary excretion of cholephilic dyes (BSP and indocyanine green). Liver injury of the cholestatic type usually decreases bilirubin excretion to a greater extent than does parenchymal cell injury.

Several studies have evaluated the effect of liver injury on the toxicity of chemicals normally excreted into bile (626, 627, 635, 1065). Results show marked differences in the effect of bile duct ligation on the LD50 of 20 xenobiotics (626). An extensive study of 175 chemicals indicated that ligation of the common bile duct and partial hepatectomy increase the adverse effects of 39 and 53 drugs, respectively (1065). The mechanism for increased toxicity after ligation of the bile duct is unclear and does not necessarily relate to the percentage of compound normally excreted into bile. For example, BSP is excreted almost exclusively via the bile, but its toxicity is not increased appreciably by ligation. In contrast, plasma concentrations of ketamine and its N-demethylated metabolite are increased prolonging ketamine sleeping time (539). If toxicity relates to the peak concentration in blood, bile duct ligation would probably have no effect. However, if toxicity relates to persistence of elevated blood levels, then ligation would be expected to have marked effects. Further work is needed to test this hypothesis.

Bile duct ligation increases diethylstilbestrol toxicity 130-fold and decreases the plasma disappearance of this steroid (627). These data indicate biliary excretion is the primary excretory pathway for diethylstilbestrol. Another hypothesis of why ligation increases toxicity of some drugs to a greater extent than others is that there could be compensatory shifts to excrete these chemicals into urine once the biliary pathway has been eliminated. In fact, increased urinary elimination of bile acid sulfates in hamsters is observed after decreased excretion by the biliary route (68). Biliary excretion of melphalan is enhanced by ligating the renal arteries (151) indicating the interrelationship of biliary and renal excretion. Similar alterations of xenobiotic excretion have been noted after reduced renal or hepatic function produced by potassium dichromate and carbon tetrachloride, respectively (231).

Bile duct ligation reduces the plasma clearance of pentobarbital and meperidine by apparently altering the initial volume of distribution. A significant reduction in perfusate flow was observed in isolated perfused liver experiments with organs from rats with previous bile duct ligation. Reduced clearance of both a high extraction drug and a lower extraction drug suggest both hepatic blood flow and drug-metabolizing activity may be altered by extrahepatic biliary tract obstruction (675).

Two-thirds hepatectomy or selective biliary obstruction and bile duct ligation affect the plasma disappearance of xenobiotics differently (635). Ligation decreased the elimination of BSP and indocyanine green to a greater extent than did partial hepatectomy, while that of PAEB and ouabain was decreased more after two-thirds hepatectomy. The data indicate that clearance of BSP and indocyanine green is more sensitive to interruption of transfer from liver to bile, while elimination of PAEB and ouabain is more dependent upon hepatic mass. Hepatic excretion of hexachlorophene was diminished by both bile duct ligation and two-thirds hepatectomy and its toxicity was markedly increased (653).

There appears to be a reserve capacity to excrete foreign compounds. Even though livers from partial hepatectomized rats weighed 40% to 45% of controls, biliary excretion of the above four drugs and bile flow rate were 60% to 65% and 80% to 90% of that of the controls (635). Further evidence of this reserve capacity was the observation of a 13-fold increase in serum bile acids 48 hours after selective biliary obstruction, and that secretion of water, bile acids, cholesterol, and phospholipids by the nonobstructed lobes was similar to con-

trols (14). This reserve capacity can be stimulated by increased substrate concentrations (14, 1092, 1235).

Bile duct ligation 24 hours before administration of a lethal dose of an extract of *Amanita phalloides* protects rats from lethality and prevents a toxin-induced increase in biliary tree permeability (372). An increase in bile flow and enlarged biliary tree capacity were observed after bile duct ligation. The mechanism for protection against phallotoxins by ligation is unclear but may result from increases in bile acid concentrations (18) or by competition with bile acids for binding sites (916) since phalloidin uptake is inhibited in cells isolated from bile duct ligated rats (1228).

Studies of the mechanism of postcholestatic choleresis after biliary obstruction indicate canalicular permeability to inulin and Na^+-K^+-ATPase activity are increased (10). Canalicular permeability is greater after administration of estrogens, phalloidin, taurolithocholate, and chlorpromazine (268, 352, 1149). These data indicate net solvent flow across tight junctions and the canalicular membrane, suggesting canalicular flow does not depend primarily on the leakiness of these barriers. This increased permeability is not a typical response of drug-induced cholestasis (928). Moreover, the enhanced Na^+-K^+-ATPase activity in livers from 3-day cholestatic rats correlates with the postobstructive choleresis (10). The hepatic content of this enzyme increases during cholestasis which suggests an adaptive response of the ATPase to complete biliary obstruction.

Liver regeneration has been studied following partial hepatectomy (722). Apparently there is an adaptive regulation involving derepression by low concentrations of solutes and also hormonal changes. Specifically, in hepatocytes isolated from 70% hepatectomized rats, there was an increase in both influx and efflux of α-aminoisobutyric acid. The amino acid transport system was Na^+-dependent and energized partly by cationic transmembrane gradients. The rapid emergence of this high affinity carrier system in the liver remnant following partial hepatectomy may be important in the regulation of liver regeneration after injury and the maintenance of xenobiotic clearance and excretion.

The effect of experimental hepatobiliary injury on drug metabolism was studied by using two surgical (selective and complete biliary obstruction) and two drug-induced (ethinylestradiol and ANIT) models. Mild injury induced by either selective obstruction or ethinylestradiol administration did not appreciably affect ^{14}C-aminopyrine elimination by $^{14}CO_2$ breath analysis or the maximal velocity of demethylation. Severe injury caused by complete obstruction and ANIT decreased $^{14}CO_2$ elimination 30% and 60%, respectively, and demethylation by 35% (1268).

Hepatobiliary function is compromised in several disease states. The total clearance of numerous drugs is reduced in patients with cirrhosis (22, 109). Biliary excretion of *d*-propranolol is reduced in cirrhotic patients because of an impaired ability of the liver to extract the drug from blood (907). Another study indicates that cirrhotic patients have increased serum concentrations and urinary elimination of bile acids (1024). Patients with chronic liver disease have a decreased clearance of bile acids (299). Excessive accumulation of copper occurs in livers of patients with primary cirrhosis (1029). Although bile acid excretion is decreased, that of copper was unaffected; this suggests that elevated copper concentrations do not occur as a result of decreased biliary excretion of the metal. Administration of the chelating agent, D-penicillamine, reduces the levels of copper and the excretion of bile acids increases toward normal rates. The mechanism for this effect is not known. In another study, patients with porphyria cutanea tarda demonstrated reduced storage and elimination of BSP. Effects may be related to derangement of porphyrin metabolism as coproporphyrin may compete with BSP for binding to ligandin and for excretion (302). In smokers, systemic bioavailability of lidocaine is decreased secondarily to an increased clearance after oral administration presumably reflecting induction of drug-metabolizing enzymes (515). In contrast, oral and systemic clearances of lidocaine are increased in patients with chronic hepatitis B. Administration of perhexiline maleate induces liver injury in patients (937) and in rats (494) which can be characterized by an impairment of the transport maximum of BSP. Additional information on the effect of liver disease on drug disposition has been reviewed (134, 1086, 1262, 1264). Interrelationship between toxicity of endotoxin and liver injury has also been discussed (854).

VIII. Enterohepatic Circulation

Numerous chemicals are secreted into bile, deposited into the intestinal lumen, reabsorbed by the intestine into the portal blood, and taken up by hepatocytes. This process is limited topographically to the liver and intestine and is aptly called the enterohepatic circulation (fig. 7). This process enables living organisms to conserve endogenous substances such as the bile acids, vitamins D_3 and B_{12}, folic acid, pyridoxine, and estrogens. Drugs also undergo enterohepatic cycling and include cardiac glycosides, chlorpromazine, indomethacin, antibiotics, cholephilic dyes, and biliary contrast media. The most physiologically important of these chemicals is the bile acids as their transport out of hepatocytes and ileocytes into bile and portal blood, respectively, is a major driving force for solute and water movement within the enterohepatic circulation. The degree of cycling of other lipophilic and hydrophilic xenobiotics depends on bile acid movement. Additional information on the enterohepatic circulation may be obtained in numerous reviews (160, 260, 497, 498, 640, 648, 926, 1101, 1107).

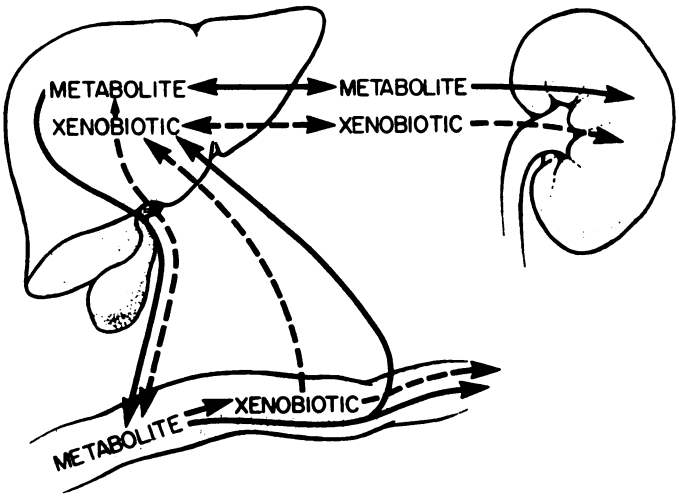

FIG. 7. Enterohepatic circulation.

A. Bile Acids

In the seventeenth century, Giovanni Borelli calculated that the total amount of bile entering the intestine was substantially greater than the quantity present in the biliary tract. In 1759, the Irish physician, Edward Barry suggested bile was reabsorbed by the intestines and returned to the liver. This prescient idea of enterohepatic cycling of bile acids was strengthened by discovery of the bile acids in 1809 by Berzelius and their enterohepatic circulation in 1937 by Sobotka and in 1941 by Josephson (490). Quantification of the enterohepatic circulation of bile acids in humans by Lindstedt's isotope dilution method indicates a 3- to 5-g bile acid pool cycles 6 to 10 times per day (744). Between 20% to 25% of this pool escapes intestinal reabsorption and is excreted in the feces (92) but endogenous synthesis from cholesterol generally equals this loss. However, details of the homeostatic mechanisms controlling synthesis, pool size, turnover frequency, bacterial metabolism, fecal loss, and bile acid secretion rates in health and disease are reviewed but are poorly understood (160).

The driving forces of the enterohepatic circulation include bile acid secretion, concentration and storage in the gallbladder, intestinal absorption, transport in portal venous blood, and hepatic uptake. Active excretion of bile acids across the canalicular membrane into bile is the primary metabolic pump for the enterohepatic circulation. This is the rate-limiting step in the transfer of bile acids from blood or de novo synthesis into bile (936). These forces within the biliary tree result in continuous production of 0.8 to 1.0 l of bile per day in intact man. However, flow fluctuates greatly and is reduced at night and stimulated with feeding.

In species with a gallbladder, bile is concentrated five- to 10-fold by active absorption of sodium and chloride ions with passive movement of water (254). In response to cephalic and hormonal influences during eating, cholecystokinin and motilin, the gallbladder contracts and extrudes up to 80% of its contents into the duodenum (319, 1113). Thus, the gallbladder is a storage organ and a mechanical pump in the enterohepatic circulation.

Bile acids are absorbed passively from all of the gastrointestinal tract via ionic and non-ionic diffusion (255). However, absorption of bile acids by non-ionic diffusion is about 10-fold greater than that of ionized species. Hence the relative contribution of each process depends on intraluminal and membrane pH, the dissociation constant (pKa) of the individual bile acid, the maximal solubilizing capacity of bile acid micelles for their own protonated forms, and the partition coefficients of the ionic and non-ionic species into absorptive membranes (160). In the upper small intestine with pH 5.5 to 6.5, about 50% of unconjugated bile acids (pKa 5.0 to 6.5) will be protonated and non-ionized; a small amount of glycine-conjugated acids (pKa 3.5 to 5.2) will be protonated; and no taurine derivatives (pKa < 1.8) will be non-ionized. To be absorbed by passive diffusion, these non-ionized bile acids must remain in solution.

The ionized bile acids, especially the taurine conjugates, depend on active sodium-coupled transport sites in the lower third of the ileum for absorption (255, 701). A reciprocal relationship exists between active and passive transport rates; the most polar bile acids with poor passive diffusion have the highest maximal transport rates across the ileum while passively absorbed bile acids have lower active transport maximums (701). Bile acids with two or more ionic substituents such as glucuronidated or sulfated derivatives (247) are poorly absorbed by either active or passive processes (407). Thus, there are three enterohepatic circuits: one fast, one intermediate, and one slow (779), as a high proportion of glycine-conjugated dihydroxy bile acids are passively absorbed in the jejunum (34, 35); taurine and glycine conjugates of di- and trihydroxy acids are actively absorbed in the distal ileum (681); and unconjugated bile acids are passively taken up in the colon (800).

All bile acids are transported back to the liver via the portal vein and only negligible concentrations are found in lymph (871). Even though the concentration of cholate and chenodeoxycholate in hepatic bile is roughly equal, portal blood is enriched with chenodeoxycholate because of its more rapid absorption in the upper small intestine and the more efficient conservation of the less polar bile acids (21, 294, 497, 498). The bile acids bind avidly to both serum albumin (294), high density lipoproteins, and perhaps low density lipoproteins (682). There is little binding to immunoglobulins or very low density lipoproteins (682). Conjugated and unconjugated bile acids bind to serum albumin at pH 7.4 with the free acid having higher binding (294).

Hepatic uptake of bile acids is extremely efficient during a single pass through the liver (497, 498, 779, 943). First-pass clearance in animals and humans is greater than 90% for cholates and between 75% to 80% for chenodeoxycholates and deoxycholates. Fractional

uptake of bile acids is independent of their perfusate level suggesting the liver's capacity to extract bile acids exceeds the transport maximum into bile (936). Hepatic uptake of bile acids usually functions with concentrations well below V_{max}. Cholates are rapidly cleared and chenodeoxycholates are cleared more slowly, suggesting that uptake is directly related to the polarity of the bile acid and may also be inversely related to the strength of binding to albumin and lipoproteins (497, 498, 528, 529, 682, 779, 1013). Details regarding the mechanism of bile acid uptake may be found in an earlier section (VI, C1) of this review.

B. Other Endogenous Compounds

Several endogenous substances other than bile acids are secreted into bile and undergo enterohepatic circulation. Bile is the major excretory route for 1,25-dihydroxyvitamin D_3 and its metabolites (46, 87, 745, 881). Enterohepatic recycling of 25-hydroxyvitamin D_3 has been demonstrated in man (43) and for 1,25- (693, 745, 1260) and 24,25-dihydroxyvitamin D_3 (692) in the rat and man. Prostacyclin and several metabolites are excreted into bile after *p*-oxidation and glucuronidation and seem to undergo enterohepatic circulation (1167). The coenzyme 5-methyltetrahydrofolate undergoes carrier-mediated hepatic uptake, secretion into bile against a high concentration gradient, and enterohepatic cycling (1131, 1151). Enterohepatic circulations have been demonstrated for pregnenolone and its 3-sulfate, deoxycorticosterone and corticosterone (304), hydroxycortisone and its metabolites (1286), norethindrone (1257), androsterone, (781) and estrone (814). All of these compounds are metabolized and are excreted predominantly as either glucuronide or sulfate conjugates.

C. Xenobiotics

Although foreign compounds undergo enterohepatic cycling, few are actively reabsorbed in the intestine. Compounds secreted into bile in lipid-soluble forms are reabsorbed by passive diffusion. Generally, these substances are biotransformed and conjugated before excretion. In this more polar form, these chemicals have insufficient lipid solubility to undergo passive diffusion. However, many compounds excreted as polar conjugates of glucuronic acid or sulfate may be hydrolyzed by bacterial β-glucuronidases or sulfatases present in bacterial flora (532), and the aglycone may be taken up into the portal circulation (1107, 1266).

Examples of xenobiotics that undergo enterohepatic recirculation include estradiol, mestranol and ethinylestradiol (140, 751), norethisterone (48), estrone-sulfate (49), propachlor (55, 713), aniline mustard (183), diclofenac (1188), fenclofenac (417), morphine (898), phenolphthalein (206, 898), diphenylacetic acid (898), 2-acetamido-4-(chloromethyl)thiazole (56), pentachloromethylthiobenzene (54), 3-phenoxybenzoic acid (514), warfarin (975), 7,12-dimethylbenz(a)anthracene (603), benzo(a)pyrene (182), chlordecone (448), numerous insecticides (776, 783), 3,4,4′-trichlorocarbanilide (482), oxazepam (99), lormetazepam (391), spironolactone (9), diethylstilbestrol (345, 457), diphenylhydantoin (295, 296), metronidazole (712), l-α-acetylmethadol (996, 997), adriamycin (1163), and sulindac (270, 271). The enterohepatic circulation of morphine, methadone, etorphine, digitoxin, diethylstilbestrol, indomethacin, glutethimide, amphetamine, and others have been reviewed (926).

Some heavy metals have been shown to undergo an enterohepatic circulation (644). For example, 25% of an intravenous dose of arsenic is excreted into feces within 2 hours, yet less than 10% is in the feces within 1 week (633). Approximately 35%, 21%, and 17% of the divalent cations of manganese, mercury, and copper, respectively, are reabsorbed after biliary excretion (191). In addition, the organic mercurials, phenyl- and methyl-mercury, have a lower recycling than inorganic mercury (197).

It has been suggested the long pharmacological half-life of digitoxin in humans results from its enterohepatic recycling (592, 593, 869). Although interrruption of this circulation leads to a reduced half-life, factors other than enterohepatic circulation are important in the slow elimination of digitoxin (1142).

Large species variations exist in the biliary excretion of many xenobiotics and animal studies do not always reflect the human situation. The investigation of enterohepatic cycling in humans has been limited to only a few drugs because of difficulties associated with prolonged interruption of the enterohepatic circulation.

D. Factors Influencing Enterohepatic Cycling

1. Binding Agents. Administration of activated charcoal or anion-exchange resins can decrease enterohepatic cycling of xenobiotics and can be clinically useful. Cholestyramine treatment of patients receiving ^{3}H-digitoxin decreases the serum half-life from 11.5 to 6.6 days (155). Similar results have been obtained with chlordecone (129, 204), phenoprocoumon (799), and bile acids (561). In fact, bile acid depletion by cholestyramine has been shown to decrease the biliary excretion of numerous organic anions including BSP, bromcresol green, indocyanine green, rose bengal, and eosine (421). Cholestyramine-induced interruption of enterohepatic cycling produces a two- and seven-fold increase in the fecal excretions of phenprocoumon and chlordecone, respectively (129, 204, 799). Activated charcoal has also been used to trap drugs in the gastrointestinal tract after their biliary excretion. Although peak blood levels are not affected significantly, charcoal reduces the serum half-life of phenylbutazone, phenobarbital, and carbamazepine (847). Administration of a polythiol-binding resin to mice greatly increases the fecal excretion and reduces the body burden of methylmercury (202). This resin was therapeutically beneficial in enhancing methylmercury excretion in an exposed Iraqi population (53). Thus, use

of these binding agents is a practical means for detoxication of animals and patients exposed to toxicants.

More recent studies indicate administration of aliphatic hydrocarbons such as mineral oil and hexadecane, which are poorly absorbed by the gut, can enhance the fecal excretion of lipophilic xenobiotics. For example, presence of 5% mineral oil in the diet of rhesus monkeys resulted in a 50% increase in the fecal excretion of mirex (1010), 2,4,5,2′,4′,5′-hexabromobiphenyl (1008), and hexachlorobenzene (1006). Similar results have been observed after 4% cholestyramine for pentachlorophenol (1009) and hexadecane for hexachlorobenzene in rats and rhesus monkeys (1005, 1006). Mineral oil and hexadecane also decreased the body burden of hexachlorobenzene in sheep (1007) presumably by trapping these agents in the feces.

Similar cycling probably exists for many therapeutic agents but the relative importance to the pharmacodynamics of each drug will have to await experimental investigation in humans. Use of binding agents in the treatment of xenobiotic toxicity is efficacious, and may, in fact, further our understanding of the biliary excretory processes and enterohepatic circulation of drugs and toxicants in humans.

2. *Antibiotics.* Although hepatic biotransformation to more polar forms decreases the enterohepatic circulation, intestinal bacteria are sometimes able to convert xenobiotics back into their lipid-soluble forms and enhance reabsorption (1106, 1266). Alterations in intestinal flora with antibiotics may decrease the enterohepatic circulation of some xenobiotics and concurrently shorten their pharmacological half-lives. Use of antibiotics in studies of the enterohepatic cycling of xenobiotics has been reviewed by Illing (532). Specific examples of decreased hydrolysis of conjugates and enterohepatic circulation of the parent compound correlate with decreased numbers of microflora and last 3 to 4 days with rifampicin or 7 to 14 days with ampicillin (48). These two antibiotics are excreted into bile and may undergo an enterohepatic recirculation (1107). Numerous studies have demonstrated that microorganisms are capable of performing appropriate biotransformations in vivo and in vitro (532).

IX. Concluding Remarks

Much new data have been published recently which greatly expand our understanding of biliary excretion. However, this knowledge about hepatic elimination lags behind that regarding mechanisms of secretion of compounds by the kidney and hepatic and renal biotransformation. Major obstacles hindering our search for new information include the relative inaccessibility of bile which deters examinations in humans and our technical inability to sample bile at various places in the liver, particularly the canaliculus. Unfortunately, we still do not completely comprehend the mechanisms of bile formation which would aid our understanding of biliary excretion and cholestasis. Despite these limitations, considerable information has been gathered about factors influencing biliary excretion and mechanisms of hepatic uptake. A major thrust in current and future research will be to utilize sophisticated biochemical techniques to isolate and purify the putative carriers involved in both hepatic uptake and biliary excretion. The myriad data discussed herein indicate the enormous complexity of hepatic function. Future efforts must isolate and characterize these carriers and ascertain how these are functionally regulated. The road to new knowledge is open and considerable efforts should be expended to further our comprehension of regulatory and functional events that occur at the cellular level.

Acknowledgments. Preparation of this review was supported in part by funds from the United States Public Health Service grants ES-03192, ES-01142, ES-07079, and S07 RR 5371, and the Burroughs Wellcome Fund. The authors express their appreciation to Drs. Zoltan Gregus, Gabriel L. Plaa, Juerg Reichen, and Mary Vore for their critical evaluation of this manuscript and valuable suggestions, and to Roxanne Southwick, Betty Saggart, Maxine Floyd, Paul Kraus, and Mae Bay for their excellent clerical assistance.

REFERENCES

1. Abel, J. J., and Rowntree, L. G.: On the pharmacological action of some phthaleins and their derivatives, with especial reference to their behavior as purgatives. J. Pharmacol. Exp. Ther. **1:** 231–264, 1909.
2. Abernathy, C. O., Ezekiel, M., and Zimmerman, H. J.: Cholestatic effects of cis-chlorprothixene on the perfused rat liver. Pharmacology **17:** 69–78, 1978.
3. Abernathy, C. O., Ezekiel, M., and Zimmerman, H. J.: Effects of some thioxanthenes on bile formation and organic anion clearance in the perfused liver rat. Arch. Int. Pharmacodyn. Ther. **234:** 193–204, 1978.
4. Abernathy, C. O., Lukacs, L., and Zimmerman, H. J.: Toxicity of tricyclic antidepressants to isolated rat hepatocytes. Biochem. Pharmacol. **24:** 347–350, 1975.
5. Abernathy, C. O., Smith, S., and Zimmerman, H. J.: The effect of chlordiazepoxide hydrochloride on the isolated perfused rat liver. Proc. Soc. Exp. Biol. Med. **149:** 271–274, 1975.
6. Abernathy, C. O., and Zimmerman, H. J.: The toxicity of thioxanthene neuroleptics to isolated rat liver cells. Proc. Soc. Exp. Biol. Med. **150:** 385–389, 1975.
7. Abou-El-Makarem, M. M., Millburn, P., Smith, R. L., and Williams, R. T.: Biliary excretion of foreign compounds: Benzene derivatives in the rat. Biochem. J. **105:** 1269, 1967.
8. Abou-El-Makarem, M. M., Millburn, P., Smith, R. L., and Williams, R. T.: Biliary excretion of foreign compounds: Species differences in biliary excretion. Biochem. J. **105:** 1289, 1967.
9. Abshagen, U., Von Grodzicki, U., Hirschberger, U., and Rennekamp, H.: Effect of enterohepatic circulation on the pharmacokinetics of spironolactone in man. Naunyn-Schmiedeberg's Arch. Pharmacol. **300:** 281–287, 1977.
10. Accatino, L., Contreras, A., Berdichevsky, E., and Quintana, C.: The effect of complete biliary obstruction on bile secretion. J. Lab. Clin. Med. **97:** 525–534, 1981.
11. Accatino, L., and Simon, F. R.: Identification and characterization of a bile acid receptor in isolated liver surface membranes. J. Clin. Invest. **57:** 496–508, 1976.
12. Acocella, G., Nicolis, F. B., and Tenconi, L. T.: The effect of an intravenous infusion of rifamycin SV on the excretion of bilirubin, bromsulphalein and indocyanine green in man. Gastroenterology **49:** 521–525, 1965.
13. Adler, R. D., Bennion, L. J., Duane, W. C., and Grundy, S. M.: Effects of low dose chenodeoxycholic acid feeding on biliary lipid metabolism. Gastroenterology **68:** 326–334, 1975.
14. Adler, R. D., Wannagat, F. J., and Ockner, R. K.: Bile secretion in selective biliary obstruction: Adaptation of taurocholate transport maximum to increased secretory load in the rat. Gastroenterology **73:** 129–136, 1977.
15. Adlercreutz, H., and Luukkainen, T.: Biochemical and clinical aspects of the enterohepatic circulation of oestrogens. Acta Endocrinol. (suppl.) **124:** 101–140, 1967.
16. Adlercreutz, H., Tikkanen, M. J., Wichmann, K., Svanborg, A., and Anberg, A.: Recurrent jaundice in pregnancy. IV. Quantitative determination of urinary and biliary estrogens, including studies in pruritus gravidarum. J. Clin. Endocrinol. Metab. **38:** 51–57, 1974.

17. ADMIRAND, W. H., AND SMALL, D. M.: The physicochemical basis of cholesterol gallstone formation in man. J. Clin. Invest. **47:** 1043–1052, 1968.
18. AGOSTINI, B., GOVINDAN, V. M., HOFMANN, W., AND WIELAND, T.: Phalloidin-induced proliferation of actin filaments within rat hepatocytes. Visualization by electron microscopy and immunofluorescence. Z. Naturforsch. **30:** 793–795, 1975.
19. AGOSTINI, B., AND HOFMANN, W.: Morphology of phalloidin intoxication. *In* Membrane Alterations as Basis of Liver Injury, ed. by H. Popper, L. Bianchi, and W. Reutter, pp. 277–292, MTP Press, Lancaster, 1977.
20. AGOSTONI, S., HOUWERTJES, M. C., AND SALT, P. J.: A new method for studying the relationship between hepatic uptake of drugs and their pharmacodynamic effects in anaesthetized cats. Br. J. Pharmacol. **68:** 637–643, 1980.
21. AHLBERG, J., ANGELIN, B., BJORKHEM, I., AND EINARSSON, K.: Individual bile acids in portal venous and systemic blood serum of fasting man. Gastroenterology **73:** 1377–1382, 1977.
22. AHMAD, N., AND BLACK, M.: The hepatic microsomal mixed-function oxidase system in man: Cofactor effects and the influence of cholestasis. J. Pharmacol. Exp. Ther. **203:** 397–408, 1977.
23. AKERBOOM, T. P. M., BILZER, M., AND SIES, H.: Competition between transport of glutathione disulfide (GSSG) and glutathione S-conjugates from perfused rat liver into bile. FEBS Lett. **140:** 73–76, 1982.
24. AKERBOOM, T. P. M., BILZER, M., AND SIES, H.: The relationship of biliary glutathione disulfide efflux and intracellular glutathione disulfide content in perfused rat liver. J. Biol. Chem. **257:** 4248–4252, 1982.
25. ALEKSANDROWICZ, Z., AND SWIERCZYNSKI, J.: The inhibition by bromothymol blue of anion translocation across the mitochondrial membrane. Biochim. Biophys. Acta **382:** 92–105, 1975.
26. ALEXANDER, J., AND AASETH, J.: Biliary excretion of copper and zinc in the rat as influenced by diethylmaleate, selenite and diethyldithiocarbamate. Biochem. Pharmacol. **29:** 2129–2133, 1980.
27. ALEXANDER, J., AND AASETH, J.: Hepatobiliary transport and organ distribution of silver in the rat as influenced by selenite. Toxicology **21:** 179–186, 1981.
28. ALEXANDER, J., AASETH, J., AND REFSVIK, T.: Excretion of zinc in rat bile—a role of glutathione. Acta Pharmacol. Toxicol. **49:** 190–194, 1981.
29. ALEXANDER, J., HOSTMARK, A. T., FORRE, O., AND VON KRAMER BRYN, M.: The influence of selenium on methyl mercury toxicity in rat hepatoma cells, human embryonic fibroblasts and human lymphocytes in culture. Acta Pharmacol. Toxicol. **45:** 379–386, 1979.
30. ALEXANDER, J., AND NORSETH, T.: The effect of selenium on the biliary excretion and organ distribution of mercury in the rat after exposure to methyl mercuric chloride. Acta Pharmacol. Toxicol. **44:** 168–176, 1979.
31. ALKALAY, D., KHEMANI, L., WAGNER, W. E., AND BARTLETT, M. F.: Sublingual and oral administration of methyltestosterone. A comparison of drug bioavailability. J. Clin. Pharmacol. **13:** 142–151, 1973.
32. ALPERT, S., MOSHER, M., SHANSKE, A., AND ARIAS, I. M.: Multiplicity of hepatic excretory mechanisms for organic anions. J. Gen. Physiol. **53:** 238–247, 1969.
33. ANDREWS, W. H. H.: Liver, University Park Press, Baltimore, MD, 1979.
34. ANGELIN, B., AND BJORKHEM, I.: Postprandial serum bile acids in healthy man. Evidence for differences in absorptive pattern between individual bile acids. Gut **18:** 606–609, 1977.
35. ANGELIN, B., BJORKHEM, I., EINARSSON, K., AND EWERTH, S.: Hepatic uptake of bile acids in man. Fasting and postprandial concentrations of individual bile acids in portal venous and systemic blood serum. J. Clin. Invest. **70:** 724–731, 1982.
36. ANGELIN, B., EINARSSON, K., AND HELLSTROM, K.: Evidence for the absorption of bile acids in the proximal small intestine of normal and hyperlipidaemic subjects. Gut **17:** 420–425, 1976.
37. ANWER, M. S., GRONWALL, R. R., ENGELKING, L. R., AND KLENTZ, R. D.: Bile acid kinetics and bile secretion in the pony. Am. J. Physiol. **229:** 592–597, 1975.
38. ANWER, M. S., AND HEGNER, D.: Effect of Na^+ on bile acid uptake by isolated rat hepatocytes. Hoppe-Seylers Z. Physiol. Chem. **359:** 181–192, 1978.
39. ANWER, M. S., KROKER, R., AND HEGNER, D.: Cholic acid uptake into isolated rat hepatocytes. Hoppe-Seylers Z. Physiol. Chem. **357:** 1477–1486, 1976.
40. ANWER, M. S., KROKER, R., AND HEGNER, D.: Effect of albumin on bile acid uptake by isolated rat hepatocytes. Is there a common bile acid carrier? Biochem. Biophys. Res. Commun. **73:** 63–71, 1976.
41. ANWER, M. S., KROKER, R., AND HEGNER, D.: Inhibition of hepatic uptake of bile acids by rifamycins. Naunyn-Schmiedeberg's Arch. Pharmacol. **302:** 19–24, 1978.
42. ARIAS, I. M., JOHNSON, L., AND WOLFSON, S.: Biliary excretion of injected conjugated and unconjugated bilirubin by normal and Gunn rats. Am. J. Physiol. **200:** 1091–1094, 1961.
43. ARNAUD, S. B., GOLDSMITH, R. S., LAMBERT, P. W., AND GO, V. L. W.: 25-Hydroxyvitamin D_3: Evidence of an enterohepatic circulation in man. Proc. Soc. Exp. Biol. Med. **149:** 570–572, 1975.
44. ARNOLD, W., MULLER, O., VON MAYERSBACH, H., AND MITRENGA, D.: The fate of injected human IgG in the mouse liver. Uptake, immunological inactivation and lysosomal reaction. Cell Tissue Res. **156:** 359–376, 1975.
45. ASHTON, M., CLARK, B., JONES, K., MOSS, G., NEALE, M., AND RITCHIE, J.: The absorption, metabolism and excretion of disodium cromoglycate in nine animal species. Toxicol. Appl. Pharmacol. **26:** 319–328, 1973.
46. AVIOLI, L. V., LEE, S. W., MCDONALD, J. E., LUND, J., AND DELUCA, H. F.: Metabolism of vitamin D-^{3}H in human subjects: Distribution in blood, bile, feces, and urine. J. Clin. Invest. **46:** 983–992, 1967.
47. BACHRACH, W. H., AND HOFMANN, A. F.: Ursodeoxycholic acid in the treatment of cholesterol cholelithiasis. Dig. Dis. Sci. **27:** 737–761, 833–856, 1982.
48. BACK, D. J., BRECKENRIDGE, A. M., CRAWFORD, F. E., CROSS, K. J., ORME, M. L'E., PERCIVAL, A., AND ROWE, P. H.: Reduction of the enterohepatic circulation of norethisterone by antibiotics in the rat—correlation with changes in the gut flora. J. Steroid Biochem. **13:** 95–100, 1980.
49. BACK, D. J., CHAPMAN, R. C., MAY, S. A., AND ROWE, P. H.: Estrone sulfate from the gastrointestinal tract of the rat. J. Steroid Biochem. **14:** 347–356, 1981.
50. BAILEY, C., FLATT, P., ATKINS, T., AND MATTY, A.: Immunoreactive insulin in bile and pancreatic juice of the rat. Endocrinol. Exp. **10:** 101–111, 1976.
51. BAKER, A. L., AND KAPLAN, M. M.: Effects of cholera enterotoxin, glucagon and dibutyryl cyclic AMP on rat liver alkaline phosphatase, bile flow, and bile composition. Gastroenterology **70:** 577–581, 1976.
52. BAKER, A. L., WOOD, R. A. B., MOOSSA, A. R., AND BOYER, J. L.: Sodium taurocholate modifies the bile acid-independent fraction of canalicular bile flow in the rhesus monkey. J. Clin. Invest. **64:** 312–320, 1979.
53. BAKIR, F., DAMLUJI, S. F., AMIN-ZAKI, L., MURTADHA, M., KHALIDI, A., AL-RAWI, N. Y., TIKRITI, S., DHAHIR, H. I., CLARKSON, T. W., SMITH, J. C., AND DOHERTY, R. A.: Methylmercury poisoning in Iraq. Science **181:** 230–241, 1973.
54. BAKKE, J. E., ASCHBACHER, P. W., FEIL, V. J., AND GUSTAFSSON, B. E.: The metabolism of pentachloromethylthiobenzene in germfree and conventional rats. Xenobiotica **11:** 173–178, 1981.
55. BAKKE, J. E., RAFTER, J., LARSEN, G. L., GUSTAFSSON, J. A., AND GUSTAFSSON, B. E.: Enterohepatic circulation of the mercapturic acid and cysteine conjugates of propachlor. Drug Metab. Dispos. **9:** 525–528, 1981.
56. BAKKE, J. E., RAFTER, J. J., LINDESKOG, P., FEIL, V. J., GUSTAFSSON, J.-A., AND GUSTAFSSON, B. E.: Metabolism of 2-acetamido-4-(chloromethyl) thiazole in germfree and conventional rats. Biochem. Pharmacol. **30:** 1839–1844, 1981.
57. BALABAUD, C.: Circadian rhythm of bile secretion in the rat. Experientia (Basel) **31:** 1299, 1975.
58. BALABAUD, C., KRON, K. A., AND GUMUCIO, J. J.: The assessment of the bile salt-nondependent fraction of canalicular bile water in the rat. J. Lab. Clin. Med. **89:** 393–399, 1977.
59. BALABAUD, C., NOEL, M., BERAUD, C., AND DANGOUMAU, J.: Circadian rhythm of bile secretion in the rat. Experientia (Basel) **31:** 1299–1300, 1975.
60. BALDWIN, J., HEER, F. W., ALBO, R., PELOSO, O., RUBY, L., AND SILEN, W.: Effect of vagus nerve stimulation on hepatic secretion of bile in human subjects. Am. J. Surg. **111:** 66–69, 1966.
61. BALINT, J. A., BEELER, D. A., KYRIAKIDES, E. C., AND TREBLE, D. H.: The effect of bile salts upon lecithin synthesis. J. Lab. Clin. Med. **77:** 122–133, 1971.
62. BALLATORI, N., AND CLARKSON, T. W.: Developmental changes in the biliary excretion of methylmercury and glutathione. Science **216:** 61–63, 1982.
63. BALLATORI, N., AND CLARKSON, T. W.: Biliary secretion of inorganic mercury. I. the chemical form of the mercury complex in rat bile. Toxicologist **3:** 138, 1983.
64. BARBARA, L., RODA, E., RODA, A., SAMA, C., FESTI, D., MAZZELLA, G., AND ALDINI, R.: The medical treatment of cholesterol gallstones: Experience with chenodeoxycholic acid. Digestion **14:** 209–219, 1976.
65. BARBER-RILEY, G.: Measurement of capacity of biliary tree in rats. Am. J. Physiol. **205:** 1122–1126, 1963.
66. BARFORD, P. A., OLAVESEN, A. H., CURTIS, C. G., AND POWELL, G. M.: Biliary excretion of some anionic derivatives of diethylstilboestrol and phenolphthalein in the guinea pig. Biochem. J. **168:** 373–377, 1977.
67. BARFORD, P. A., OLAVESEN, A. H., CURTIS, C. G., AND POWELL, G. M.: Metabolic fates of diethylstilboestrol sulphates in the rat. Biochem. J. **164:** 423–430, 1977.
68. BARNES, S., BURHOL, P. G., ZANDER, R., AND HISRSCHOWITZ, B. I.: The effect of bile duct ligation on hepatic bile acid sulfotransferase activity in the hamster. Biochem. Med. **22:** 165–174, 1979.
69. BARNHART, J. L., AND CLARENBERG, R.: Factors determining clearance of bilirubin in perfused rat liver. Am. J. Physiol. **225:** 497–507, 1973.
70. BARNHART, J. L., AND COMBES, B.: Characteristics common to choleretic increments of bile induced by theophylline, glucagon and SQ-20009 in the dog. Proc. Soc. Exp. Biol. Med. **150:** 591–596, 1975.
71. BARNHART, J. L., AND COMBES, B.: Biliary excretion of dye in dogs infused with BSP or its glutathione conjugate. Am. J. Physiol. **231:** 399–407, 1976.

72. BARNHART, J. L., AND COMBES, B.: Characterization of SC2644-induced choleresis in the dog. Evidence for canalicular bicarbonate secretion. J. Pharmacol. Exp. Ther. **206:** 190–197, 1978.
73. BARNHART, J. L., AND COMBES, B.: Choleresis associated with metabolism and biliary excretion of diethyl maleate in the rat and dog. J. Pharmacol. Exp. Ther. **206:** 614–623, 1978.
74. BARNHART, J. L., AND COMBES, B.: Erythritol and mannitol clearances with taurocholate and secretin-induced cholereses. Am. J. Physiol. **234:** E146–E156, 1978.
75. BARNHART, J. L., AND COMBES, B.: Apparent volume of the biliary tree in the dog. Can. J. Physiol. Pharmacol. **57:** 524–528, 1979.
76. BARNHART, J. L., GRONWALL, R. R., AND COMBES, B.: Biliary excretion of sulfobromophthalein compounds in normal and mutant Corriedale sheep. Evidence for a disproportionate transport defect for conjugated sulfobromophthalein. Hepatology **1:** 441–447, 1981.
77. BARNHART, J. L., AND UPSON, D. W.: Bile flow and electrolyte composition of bile associated with maximum bilirubin excretion in sheep. Can. J. Physiol. Pharmacol. **57:** 710–716, 1979.
78. BARRETT, P. V. D.: Hyperbilirubinemia of fasting. J.A.M.A. **217:** 1349–1353, 1971.
79. BASSAN, H., KENDLER, J., HARINASUTA, U., AND ZIMMERMAN, H. J.: Effects of an anabolic steroid (Norbolethone) on the function of the isolated perfused rat liver. Biochem. Pharmacol. **20:** 1429–1435, 1971.
80. BAUR, H., AND HELDT, H. W.: Transport of hexoses across the liver-cell membrane. Eur. J. Biochem. **74:** 397–403, 1977.
81. BAUR, H., KASPEREK, S., AND PFAFF, E.: Criteria of viability of isolated liver cells. Hoppe-Seylers Z. Physiol. Chem. **356:** 827–838, 1975.
82. BEAUBIEN, A. R., AND PAKUTS, A. P.: Influence of dose on first-pass kinetics of 14-C-imipramine in the isolated perfused rat liver. Drug Metab. Dispos. **7:** 34–39, 1979.
83. BECKER, B. A., AND PLAA, G. L.: The nature of α-naphthylisothiocyanate-induced cholestasis. Toxicol. Appl. Pharmacol. **7:** 680–685, 1965.
84. BECKER, B. A., AND PLAA, G. L.: Quantitative and temporal delineation of various parameters of liver dysfunction due to α-naphthylisothiocyanate. Toxicol. Appl. Pharmacol. **7:** 708–718, 1965.
85. BECKER, F. F.: The liver: Normal and abnormal functions. Part A and Part B, Marcel Dekker, New York, 1974, 1975.
86. BELL, G. D., MCMULLIN, J., DORAN, J., OLIVER, J., MCALLISTER, J., MONKS, A., AND RICHENS, A.: Ioglycamide (Biligram) studies in man: Plasma binding, renal and biliary excretion studies in jaundiced and anicteric patients. Br. J. Radiol. **51:** 251, 1978.
87. BELL, P. A., AND KODICEK, E.: Investigations on metabolites of vitamin D in rat bile. Biochem. J. **115:** 663–669, 1969.
88. BENNION, L., AND GRUNDY, S.: Risk factors for the development of cholelithiasis in man. N. Engl. J. Med. **299:** 1161–1167, 1978.
89. BERGERON, J. J., LEVINE, M. G., SIKSTROM, R., O'SHAUGHNESSY, D., KOPRIWA, B., NADLER, N. J., AND POSNER, B. I.: Polypeptide hormone binding sites in vivo: Initial localization of ^{125}I-labeled insulin to hepatocyte plasmalemma as visualized by electron microscope radioautography. Proc. Natl. Acad. Sci. U.S.A. **74:** 5051–5055, 1977.
90. BERGERON, J. J. M., SIKSTROM, R., HAND, A. R., AND POSNER, B. I.: Binding and uptake of ^{125}I-insulin into rat liver hepatocytes and endothelium. An in vivo radioautographic study. J. Cell Biol. **80:** 427–443, 1979.
91. BERGMAN, F., AND VAN DER LINDEN, W.: Liver morphology and gallstone formation in hamsters and mice treated with chenodeoxycholic acid. Acta Pathol. Microbiol. Scand. **81:** 213–221, 1973.
92. BERGSTROM, S.: Metabolism of bile acids. Fed. Proc. **21:** 28–32, 1962.
93. BERK, P. D., BLOOMER, J. R., HOWE, R. B., AND BERLIN, N. I.: Constitutional hepatic dysfunction (Gilbert's syndrome). Am. J. Med. **49:** 296–305, 1970.
94. BERK, R. N., GOLDBERGER, L. E., AND LOEB, D. M.: The role of bile salts in the hepatic excretion of iopanoic acid. Invest. Radiol. **9:** 7–15, 1974.
95. BERK, R. N., LOEB, P. M., AND COBO-FRENKEL, A.: The biliary and urinary excretion of sodium tyropanoate and sodium ipodate in dogs: Pharmacokinetics, influence of bile salts and choleretic effects with comparison to iopanoic acid. Invest. Radiol. **12:** 85–95, 1977.
96. BERK, R. N., LOEB, P. M., COBO-FRENKEL, A., AND BARNHART, J. L.: The biliary and urinary excretion of iopanoic acid: Pharmacokinetics, influence of bile salts, and choleretic effect. Radiology **120:** 41–47, 1976.
97. BERNDT, W. O., MUDGE, G. H., AND WADE, D. N.: Hepatic slice accumulation of iopanoic and iophenoxic acids. J. Pharmacol. Exp. Ther. **179:** 85–90, 1971.
98. BERRY, M. N., AND FRIEND, D. S.: High yield preparation of isolated rat liver parenchymal cells; a biochemical and fine structural study. J. Cell Biol. **43:** 506–520, 1969.
99. BERTAGNI, P., BIANCHI, R., MARCUCCI, F., MISSINI, E., AND GARATTIN, S.: The enterohepatic circulation of oxazepam-O-glucuronide in guinea-pigs. J. Pharm. Pharmacol. **30:** 185–186, 1978.
100. BERTAGNI, P., HIROM, P. C., MILLBURN, P., OSIYEMI, F. O., SMITH, R. L., TURBERT, H. B., AND WILLIAMS, R. T.: Sex and species differences in the biliary excretion of tartrazine and lissamine fast yellow in the rat, guinea-pig and rabbit. The influence of sex hormones on tartrazine excretion in the rat. J. Pharm. Pharmacol. **24:** 620–624, 1972.
101. BERTHELOT, P.: Mechanisms and prediction of drug-induced liver disease. Gut **14:** 332–339, 1973.
102. BERTHELOT, P., ERLINGER, S., DHUMEAUX, D., AND PREAUX, A.-M.: Mechanism of phenobarbital-induced hypercholeresis in the rat. Am. J. Physiol. **219:** 809–813, 1970.
103. BHARGAVA, M., LISTOWSKY, I., AND ARIAS, I. M.: Bilirubin binding and glutathione-S-transferase activity are independent processes. J. Biol. Chem. **253:** 4112–4115, 1978.
104. BIAVA, C.: Studies on cholestasis: The fine structure and morphogenesis of hepatocellular and canalicular bile pigment. Lab. Invest. **13:** 1099–1123, 1964.
105. BINDER, H. J., AND BOYER, J. L.: Bile salts: A determinant of the bile peritoneal electrical potential difference in the rat. Gastroenterology **65:** 943–948, 1973.
106. BINET, S., DELAGE, Y., AND ERLINGER, S.: Influence of taurocholate, taurochenodeoxycholate, and taurodehydrocholate on sulfobromophthalein transport into bile. Am. J. Physiol. **236:** E10–E14, 1979.
107. BIRBECK, M. S. C., CARTWRIGHT, P., HALL, J. G., ORLANS, E., AND PEPPARD, J.: The transport by hepatocytes of immunoglobulin A from blood to bile visualized by autoradiography and electron microscopy. Immunology **37:** 477–484, 1979.
108. BIRKETT, C. R., COULSON, C., POGSON, C. I., AND GULL, K.: Inhibition of secretion of proteins and triacylglycerol from isolated rat hepatocytes mediated by benzimidazole carbamate antimicrotubule agents. Biochem. Pharmacol. **30:** 1629–1633, 1981.
109. BLACK, M., AND ARIAS, I. M.: Pharmacological considerations in liver disease. *In* Diseases of the Liver, 4th ed., ed. by L. Schiff, pp. 755–773, J. B. Lippincott, Philadelphia, 1975.
110. BLANCKAERT, N., GOLLAN, J., AND SCHMID, R.: Bilirubin diglucuronide synthesis by a UDP-glucuronic acid-dependent enzyme system in rat liver microsomes. Proc. Natl. Acad. Sci. U.S.A. **76:** 2037–2041, 1979.
111. BLANCKAERT, N., GOLLAN, J., AND SCHMID, R.: Mechanism of bilirubin diglucuronide formation in intact rats. J. Clin. Invest. **65:** 1332–1342, 1980.
112. BLAXTER, K. L., AND COWIE, A. T.: Excretion of lead in the bile. Nature (Lond.) **157:** 588, 1946.
113. BLITZER, B. L., AND BOYER, J. L.: Cytochemical localization of Na^+, K^+-ATPase in the rat hepatocyte. J. Clin. Invest. **62:** 1104–1108, 1978.
114. BLITZER, B. L., RATOOSH, S. L., DONOVAN, C. B., AND BOYER, J. L.: Effects of inhibitors of Na^+-coupled ion transport on bile acid uptake by isolated rat hepatocytes. Am. J. Physiol. **243:** G48–G53, 1982.
115. BLOM, A., KEULEMANS, K., AND MEIJER, D. K. F.: Transport of dibromosulphthalein by isolated rat hepatocytes. Biochem. Pharmacol. **30:** 1809–1816, 1981.
116. BLOM, A., SCAF, A. H. J., AND MEIJER, D. K. F.: Hepatic drug transport in the rat. A comparison between isolated hepatocytes, the isolated perfused liver and the liver in vivo. Biochem. Pharmacol. **31:** 1553–1565, 1982.
117. BLOOM, W., AND FAWCETT, D. W.: A Textbook of Histology, 9th ed., chapt. 27, W. B. Saunders Company, Philadelphia, 1968.
118. BLOOMER, J. R., BOYER, J. L., AND KLATSKIN, G.: Inhibition of bilirubin excretion in man during dehydrocholate choleresis. Gastroenterology **65:** 929–935, 1973.
119. BLOOMER, J. R., AND ZACCARIA, J.: Effect of graded bilirubin loads on bilirubin transport by perfused rat liver. Am. J. Physiol. **230:** 736–742, 1976.
120. BOND, J. A., MEDINSKY, M. A., DENT, J. G., AND RICKERT, D. E.: Sex-dependent metabolism and biliary excretion of [2,4-^{14}C] dinitrotoluene in isolated perfused rat livers. J. Pharmacol. Exp. Ther. **219:** 598–603, 1981.
121. BONIFACINO, J. S., SANCHEZ, S. H., AND PALADINI, A. C.: Characterization of human somatotropin binding to detergent-solubilized lactogenic receptors from rat liver. Biochem. J. **194:** 385–394, 1981.
122. BONVICINI, F., GAUTIER, A., GARDIOL, D., AND BOREL, G.-A.: Cholesterol in acute cholestasis induced by taurolithocholic acid. A cytochemical study in transmission and scanning electron microscopy. Lab. Invest. **38:** 487–495, 1978.
123. BOUCHIER, I. A. D.: The medical treatment of gallstones. Annu. Rev. Med. **31:** 59–77, 1980.
124. BOYER, J. L.: New concepts of mechanisms of hepatocyte bile formation. Physiol. Rev. **60:** 303–326, 1980.
125. BOYER, J. L., AND BLOOMER, J. R.: Canalicular bile secretion in man: Studies utilizing the biliary clearance of [^{14}C]mannitol. J. Clin. Invest. **54:** 773–781, 1974.
126. BOYER, J. L., ELIAS, E., AND LAYDEN, T. J.: The paracellular pathway and bile formation. Yale J. Biol. Med. **52:** 61–67, 1979.
127. BOYER, J. L., AND KLATSKIN, G.: Canalicular bile flow and bile secretory pressure: Evidence for a non-bile salt dependent fraction in the isolated perfused rat liver. Gastroenterology **59:** 853–859, 1970.
128. BOYER, J. L., SCHEIG, R. L., AND KLATSKIN, G.: The effect of sodium taurocholate on the hepatic metabolism of sulfobromophthalein sodium (BSP). The role of bile flow. J. Clin. Invest. **49:** 206–215, 1970.
129. BOYLAN, J. J., EGLE, J. L., AND GUZELIAN, P. S.: Cholestyramine: Use as a new therapeutic approach for chlordecone (Kepone) poisoning. Science **199:** 893–895, 1978.

130. BRADLEY, S. E., AND HERZ, R.: Permselectivity of biliary canalicular membrane in rat: Clearance probe analysis. Am. J. Physiol. **235:** E570–E576, 1978.
131. BRADY, F. O.: The physiological function of metallothionein. Trends Biochem. Sci. **7:** 143–145, 1982.
132. BRANCH, R. A.: Drugs as indicators of hepatic function. Hepatology **2:** 97–105, 1982.
133. BRANCH, R. A., NIES, A. S., AND SHAND, D. G.: The disposition of propanolol. VIII. General implications of the effects of liver blood flow on elimination from the perfused rat liver. Drug Metab. Dispos. **1:** 687–690, 1973.
134. BRANCH, R. A., SHAND, D. G., WILKINSON, G. R., AND NIES, A. S.: Increased clearance of antipyrine and *d*-propranolol after phenobarbital treatment in the monkey. J. Clin. Invest. **53:** 1101–1107, 1974.
135. BRAUER, R. W.: Mechanisms of bile secretion. J.A.M.A. **169:** 1462–1466, 1959.
136. BRAUER, R. W.: Hepatic blood supply and the secretion of bile. *In* The Biliary System, ed. by W. Taylor, pp. 41–67, Blackwell, Oxford, 1965.
137. BRAUER, R. W., LEONG, G. F., AND HOLLOWAY, R. J.: Mechanics of bile secretion: Effect of perfusion pressure and temperature on bile flow and secretion pressure. Am. J. Physiol. **177:** 103–112, 1954.
138. BRAUN, P.: Hepatotoxicity of erythromycin. J. Infect. Dis. **119:** 300–306, 1969.
139. BREMNER, I., AND DAVIES, N. T.: The induction of metallothionein in rat liver by zinc injection and restriction of food intake. Biochem. J. **149:** 733–738, 1975.
140. BREWSTER, D., JONES, R. S., AND SYMONS, A. M.: Effects of neomycin on the biliary excretion and enterohepatic circulation of mestranol and 17β-oestradiol. Biochem. Pharmacol. **26:** 943–946, 1977.
141. BRIGELIUS, R., AND ANWER, M. S.: Increased biliary GSSG-secretion and loss of hepatic glutathione in isolated perfused rat liver after paraquat treatment. Res. Commun. Chem. Pathol. Pharmacol. **31:** 493–502, 1981.
142. BROCK, W. J., AND VORE, M.: Hepatic morphine and estrone glucuronyltransferase activity and morphine biliary excretion in the isolated perfused rat liver. Drug Metab. Dispos. **10:** 336–343, 1982.
143. BROGARD, J. M., DORNER, M., PINGET, M., ADLOFF, M., AND LAVILLAURREIX, J.: The biliary excretion of cefazolin. J. Infect. Dis. **131:** 625–633, 1975.
144. BROGARD, J. M., PINGET, M., MEYER, C., DORNER, M., AND LAVILLAURREIX, J.: Biliary excretion of ampicillin: Experimental and clinical study. Chemotherapy **23:** 213–226, 1977.
145. BROWN, R. B., MARTYAK, S. N., BARZA, M., CURTIS, L., AND WEINSTEIN, L.: Penetration of clindamycin phosphate into the abnormal human biliary tract. Ann. Intern. Med. **84:** 168–170, 1976.
146. BROWN, W. R.: Relationships between immunoglobulins and the intestinal epithelium. Gastroenterology **75:** 129–138, 1978.
147. BUHLER, R. H. O., AND KAGI, J. H. R.: Human hepatic metallothioneins. FEBS Lett. **39:** 229–234, 1974.
148. BURCH, G. E., AND WALSH, J. J.: The excretion and biologic decay rates of Cd^{115m} with a consideration of space, mass, and distribution in dogs. J. Lab. Clin. Med. **54:** 66–72, 1959.
149. BURR, R., SCHWENK, M., AND PFAFF, E.: Interaction of bromosulfophthalein with mitochondrial membranes—inhibition of respiration. Biochem. Pharmacol. **26:** 461–466, 1977.
150. BUXTON, B. H., WITSCHI, H., AND PLAA, G. L.: Biochemical changes provoked in rat liver by cholestatic doses of α-naphthylisothiocyanate. Toxicol. Appl. Pharmacol. **24:** 60–72, 1973.
151. BYINGTON, K., BOWE, C., AND MCKINSEY, D.: Biliary excretion of melphalan by control and anuric rats. Biochem. Pharmacol. **29:** 2518–2520, 1980.
152. BYINGTON, K. H., AND HANSBROUGH, E.: Inhibition of the enzymatic activity of ligandin by organogermanium, organolead or organotin compounds and the biliary excretion of sulfobromophthalein by the rat. J. Pharmacol. Exp. Ther. **208:** 248–253, 1979.
153. CAGEN, S. Z., AND KLAASSEN, C. D.: Evaluation of hepatic storage of sulfobromophthalein in rats and dogs. Toxicology **25:** 261–270, 1982.
154. CAIN, K., AND SKILLETER, D. N.: Selective uptake of cadmium by the parenchymal cells of liver. Biochem. J. **188:** 285–288, 1980.
155. CALDWELL, J. H., BUSH, C. A., AND GREENBERGER, J. J.: Interruption of the enterohepatic circulation of digitoxin by cholestyramine. II. Effect on metabolic disposition of tritium-labeled digitoxin and cardiac systolic intervals in man. J. Clin. Invest. **20:** 2638–2644, 1971.
156. CAPIZZO, F., AND ROBERTS, R. J.: Effect of phenobarbital, chlorpromazine, actinomycin D and chronic α-naphthylisothiocyanate administration on α-naphthylisothiocyanate [14-C] disposition and α-naphthylisothiocyanate-induced hyperbilirubinemia. J. Pharmacol. Exp. Ther. **179:** 455–464, 1971.
157. CAPLE, I. W., HALPIN, C. G., AND HEATH, T.: Bile and pancreatic secretion in chickens: the effects of bile salts, feeding and acid. Comp. Biochem. Physiol. **61A:** 653–659, 1978.
158. CAPRON, J. P., DUMONT, M., FELDMANN, G., AND ERLINGER, S.: Barbiturate-induced choleresis: Possible independence from microsomal enzyme induction. Digestion **15:** 556–565, 1977.
159. CAPRON, J. P., AND ERLINGER, S.: Barbiturates and biliary function. Digestion **12:** 43–56, 1975.
160. CAREY, M. C.: The enterohepatic circulation. *In* The Liver: Biology and Pathobiology, ed. by I. Arias, H. Popper, D. Schachter, and D. A. Shafritz, chapt. 27, pp. 429–465, Raven Press, New York, 1982.
161. CAREY, M. C., AND SMALL, D. M.: Micelle formation by bile salts. Physical-chemical and thermodynamic considerations. Arch. Intern. Med. **130:** 506–527, 1972.
162. CAREY, M. C., AND SMALL, D. M.: The physical chemistry of cholesterol solubility in bile. J. Clin. Invest. **61:** 998–1026, 1978.
163. CAREY, M. C., WU, S. F. J., AND WATKINS, J. B.: Solution properties of sulfated monohydroxy bile salts. Relative insolubility of the disodium salt of glycolithocholate sulfate. Biochim. Biophys. Acta **575:** 16–26, 1979.
164. CARRELLA, M., AND COOPER, A. D.: High affinity binding of chylomicron remnants to rat liver plasma membranes. Proc. Natl. Acad. Sci. U.S.A. **76:** 338–342, 1979.
165. CARRILLO, M. C., MONTI, J. A., RODRIGUEZ, J. V., AND RODRIGUEZ-GARAY, E.: Bile flow and sulphobromophthalein biliary excretion in aflatoxin-treated rats. I.R.C.S. Med. Sci. **9:** 1156–1157, 1981.
166. CASTAGNA, M., AND CHAUVEAU, J.: Separation of metabolically distinct cell fractions from isolated rat hepatocytes. Exp. Cell Res. **57:** 211–222, 1969.
167. CASTELLINO, N., AND ALOJ, S.: Kinetics of the distribution and excretion of lead in the rat. Br. J. Ind. Med. **21:** 308–314, 1964.
168. CASTLE, M. C., AND LAGE, G. L.: Excretion of ^{3}H-digitoxin following spironolactone pretreatment in rats. Drug Metab. Dispos. **1:** 590–598, 1973.
169. CASTLE, M. C., AND LAGE, G. L.: ^{3}H-Digitoxin and its metabolites following spironolactone pretreatment. Res. Commun. Chem. Pathol. Pharmacol. **6:** 601–612, 1973.
170. CAUJOLLE, F., OUSTRIN, J., AND SILVE-MAMY, G.: Fixation et circulation enterohepatique du cadmium. J. Eur. Toxicol. **3:** 310–315, 1971.
171. CHAKRABARTI, S., AND BRODEUR, J.: Effects of microsomal induction and inhibition on styrene-induced acute hepatotoxicity in rats. J. Toxicol. Environ. Health **8:** 599–607, 1981.
172. CHAKRABARTI, S., AND BRODEUR, J.: Plasma disappearance and biliary excretion of bromosulfophthalein in styrene-treated and styrene oxide-treated rats. J. Toxicol. Environ. Health **8:** 609–617, 1981.
173. CHAO, Y. S., JONES, A. L., AND HRADEK, G. T.: Autoradiographical localization of the sites of uptake, cellular transport, and catabolism of low density lipoproteins in the liver of normal and estrogen-treated rats. Proc. Natl. Acad. Sci. U.S.A. **78:** 597–601, 1981.
174. CHELVAN, P., HAMILTON-MILLER, J. M. T., AND BRUMFITT, W.: Biliary excretion of erythromycin after parenteral administration. Br. J. Clin. Pharmacol. **8:** 233–235, 1979.
175. CHEN, C.-P., AND LEE, R. H.: Active transport of alpha-aminoisobutyric acid in freshly prepared rat hepatocytes. Life Sci. **21:** 577–584, 1977.
176. CHEN, C.-P., VU, V., AND COHEN, S.: Lidocaine uptake in isolated rat hepatocytes and effects of *dl*-propranolol. Toxicol. Appl. Pharmacol. **55:** 162–168, 1980.
177. CHENDEROVITCH, J.: Secretory function of the rabbit common bile duct. Am. J. Physiol. **223:** 695–706, 1972.
178. CHENDEROVITCH, J., RAIZMAN, A., AND INFANTE, R.: Mechanism of ethacrynic acid-induced choleresis in the rat. Am. J. Physiol. **229:** 1180–1187, 1975.
179. CHERIAN, M. G.: Biliary excretion of cadmium in rat. II. The role of metallothionein in the hepatobiliary transport of cadmium. J. Toxicol. Environ. Health **2:** 955–961, 1977.
180. CHERIAN, M. G., AND VOSTAL, J. J.: Biliary excretion of cadmium in rat. I. Dose dependent biliary excretion and the form of cadmium in the bile. J. Toxicol. Environ. Health **2:** 945–954, 1977.
181. CHERRICK, G. R., STEIN, S. W., LEEVY, C. M., AND DAVIDSON, C. S.: Indocyanine green: Observations on its physical properties, plasma decay, and hepatic extraction. J. Clin. Invest. **39:** 592–600, 1960.
182. CHIPMAN, J. K., HIROM, P. C., FROST, G. S., AND MILLBURN, P.: The biliary excretion and enterohepatic circulation of benzo(a)pyrene and its metabolites in the rat. Biochem. Pharmacol. **30:** 937–944, 1981.
183. CHIPMAN, J. K., HIROM, P. C., AND MILLBURN, P.: Biliary excretion and enterohepatic circulation of aniline mustard metabolites in the rat and the rabbit. Biochem. Pharmacol. **29:** 1299–1301, 1980.
184. CHIVRAC, D., DUMONT, M., AND ERLINGER, S.: Lack of parallelism between microsomal enzyme induction and phenobarbital-induced hypercholeresis in the rat. Digestion **17:** 516–525, 1978.
185. CHOWDHURY, J. R., AND ARIAS, I. M.: Dismutation of bilirubin monoglucuronide. *In* Enzymatic Basis of Detoxication, vol. II, ed. by W. B. Jakoby, pp. 37–42, Academic Press, New York, 1980.
186. CHOWDHURY, J. R., CHOWDHURY, N. R., GARTNER, U., WOLKOFF, A. W., AND ARIAS, I. M.: Bilirubin diglucuronide formation in intact rats and in isolated Gunn rat liver. J. Clin. Invest. **69:** 595–603, 1982.
187. CHOWDHURY, J. R., CHOWDHURY, N. R., WU, G., SHOUVAL, R., AND ARIAS, I. M.: Bilirubin mono- and diglucuronide formation by human liver in vitro: Assay by high pressure liquid chromatography. Hepatology **1:** 622–627, 1981.
188. CHRISTENSEN, H. N.: Biological Transport, 2nd ed., Benjamin, Reading, MA, 1975.

189. CHRZONSZEZEWSKY, N.: Zur anatomie und physiologie der leiber. Virchows Arch. [Pathol. Anat.] **35:** 153–165, 1866.
190. CIKRT, M.: Biliary excretion of ^{203}Hg, ^{51}Cr, ^{52}Mn, and ^{210}Pb in the rat. Br. J. Ind. Med. **29:** 74–80, 1972.
191. CIKRT, M.: Enterohepatic circulation of ^{64}Cu, ^{52}Mn, and ^{203}Hg in rats. Arch. Toxicol. **31:** 51–59, 1973.
192. CIKRT, M., AND BENCKO, V.: Biliary excretion of ^{7}Be and its distribution after intravenous administration of $^{7}BeCl_2$ in rats. Arch. Toxicol. **34:** 53–60, 1975.
193. CIKRT, M., AND HAVRDOVA, J.: Effects of dosage and cadmium pretreatment on the binding of cadmium in rat bile. Experientia (Basel) **35:** 1640–1641, 1979.
194. CIKRT, M., HAVRDOVA, J., AND TICHY, M.: Changes in the binding of copper and zinc in the rat bile during 24 hours after application. Arch. Toxicol. **32:** 321–329, 1974.
195. CIKRT, M., AND TICHY, M.: Polyacrylamide gel disc electrophoresis of rat bile after intravenous administration of $^{52}MnCl_2$, $^{64}CuCl_2$, $^{203}HgCl_2$ and $^{210}Pb(NO_3)_2$. Experientia (Basel) **28:** 383–384, 1972.
196. CIKRT, M., AND TICHY, M.: Excretion of cadmium through bile and intestinal wall in rats. Br. J. Ind. Med. **31:** 134–139, 1974.
197. CIKRT, M., AND TICHY, M.: Biliary excretion of phenyl and methyl mercury chlorides and their enterohepatic circulation in rats. Environ. Res. **8:** 71–81, 1974.
198. CIKRT, M., AND TICHY, M.: Biliary excretion of cobalt in rats. J. Hyg. Epidemiol. Microbiol. Immunol. **25:** 364–368, 1981.
199. CLARK, A. G., AND COOKE, R.: The effect of route of administration on the biliary excretion of phenolphthalein and its glucuronide. J. Pharm. Pharmacol. **30:** 382–383, 1978.
200. CLARK, A. G., HIROM, P. C., MILLBURN, P., AND SMITH, R. L.: Absorption of some organic compounds from the biliary system of the rat. J. Pharm. Pharmacol. **23:** 150–152, 1971.
201. CLARK, B., AND NEALE, M. G.: Hepatic and renal clearance of sodium cromoglycate. J. Pharm. Pharmacol. **33:** 744–745, 1981.
202. CLARKSON, T. W., SMALL, H., AND NORSETH, T.: Excretion and absorption of methyl mercury after polythiol resin treatment. Arch. Environ. Health **26:** 173–176, 1973.
203. COHEN, L., LEWIS, C., AND ARIAS, I. M.: Pregnancy, oral contraceptives, and chronic familial jaundice with predominantly conjugated hyperbilirubinemia (Dubin-Johnson syndrome). Gastroenterology **62:** 1182–1190, 1972.
204. COHN, W. J., BOYLAN, J. J., BLANKE, R. V., FARISS, M. W., HOWELL, J. R., AND GUZELIAN, P. S.: Treatment of chlordecone (Kepone) toxicity with cholestyramine. N. Engl. J. Med. **298:** 243–248, 1978.
205. COLBURN, W. A.: A pharmacokinetic model to differentiate preabsorptive, gut epithelial, and hepatic first-pass metabolism. J. Pharmacokinet. Biopharm. **7:** 407–415, 1979.
206. COLBURN, W. A., HIROM, P. C., PARKER, R. J., AND MILLBURN, P.: A pharmacokinetic model for enterohepatic recirculation in the rat: Phenolphthalein, a model drug. Drug Metab. Dispos. **7:** 100–102, 1979.
207. COLEMAN, R., IQBAL, S., GODFREY, P. P., AND BILLINGTON, D.: Membranes and bile formation: Composition of several mammalian biles and their membrane-damaging properties. Biochem. J. **178:** 201–208, 1979.
208. COMBES, B.: The importance of conjugation with glutathione for sulfobromophthalein sodium (BSP) transfer from blood to bile. J. Clin. Invest. **44:** 1214–1224, 1965.
209. COMBES, B., AND STAKELUM, G. S.: Conjugation of sulfobromophthalein sodium with glutathione in thioether linkage by the rat. J. Clin. Invest. **39:** 1214–1222, 1960.
210. COMPERNOLLE, F., VAN HEES, G. P., BLANCKAERT, N., AND HEIRWEGH, K. P. M.: Glucuronic acid conjugates of bilirubin IX in normal bile compared to obstructive bile. Transformation of the 1-O-acylglucuronide into 2-, 3-, and 4-O-acylglucuronides. Biochem. J. **171:** 185–201, 1978.
211. COOKE, W. J., BERNDT, W. O., AND MUDGE, G. H.: Effects of phenobarbital and taurocholate on biliary excretion of iopanoate and iophenoxate in the rat. J. Pharmacol. Exp. Ther. **187:** 158–168, 1973.
212. COOKE, W. J., AND COOKE, L.: Biliary excretion of iopanoate glucuronide by the rat. Drug Metab. Dispos. **5:** 368–376, 1977.
213. COOKE, W. J., AND COOKE, L.: Effects of anesthetic agents on the biliary excretion of iopanoate in the rat. Drug Metab. Dispos. **5:** 377–385, 1977.
214. COOPER, B., EAKINS, M. N., AND SLATER, T. F.: The effect of various anaesthetic techniques on the flow rate, constituents and enzymic composition of rat bile. Biochem. Pharmacol. **25:** 1711–1718, 1976.
215. CORBIC, M., DUMONT, M., DECOUET, G., AND ERLINGER, S.: Choleretic and diuretic properties of dihydroxydibutyl ether in the rat. J. Pharmacol. Exp. Ther. **221:** 769–774, 1982.
216. CORNELIUS, C. E.: Rates of choleresis in various species. Dig. Dis. **21:** 426–428, 1976.
217. CORNELIUS, C. E., AND GRONWALL, R. R.: Congenital photosensitivity and hyperbilirubinemia in Southdown sheep in the United States. Am. J. Vet. Res. **29:** 291–295, 1968.
218. CORONARY DRUG PROJECT RESEARCH GROUP. Gallbladder disease as a side effect of drugs influencing lipid metabolism. N. Engl. J. Med. **296:** 1185–1190, 1977.
219. COX, E., AND WRIGHT, S. E.: The hepatic excretion of digitalis glycosides and their genins in the rat. J. Pharmacol. Exp. Ther. **126:** 117–122, 1959.
220. COYNE, M. J., BONORRIS, G. G., CHUNG, A., GOLDSTEIN, L. I., LAHANA, D., AND SCHOENFIELD, L. J.: Treatment of gallstones with chenodeoxycholic acid and phenobarbital. N. Engl. J. Med. **292:** 604–607, 1975.
221. CRAIK, J. D., AND ELLIOTT, K. R.: Kinetics of 3-O-methyl-D-glucose transport in isolated rat hepatocytes. Biochem. J. **182:** 503–508, 1979.
222. CRAIK, J. D., AND ELLIOTT, K. R.: Transport of D-fructose and D-galactose into isolated rat hepatocytes. Biochem. J. **192:** 373–375, 1980.
223. CRONE, C.: Permeability of capillaries in various organs as determined by use of the "indicator diffusion" method. Acta Physiol. Scand. **58:** 292–305, 1963.
224. CULBERTSON, J. W., WILKINS, R. W., INGELFINGER, F. J., AND BRADLEY, S. E.: The effect of upright posture upon hepatic blood flow in normotensive and hypertensive subjects. J. Clin. Invest. **30:** 305–311, 1951.
225. CURTIS, L. R., AND MEHENDALE, H. M.: The effects of Kepone pretreatment on biliary excretion of xenobiotics in the male rat. Toxicol. Appl. Pharmacol. **47:** 295–303, 1979.
226. CURTIS, L. R., AND MEHENDALE, H. M.: Hepatobiliary dysfunction and inhibition of adenosine triphosphatase activity of bile canaliculi-enriched fractions following in vivo mirex, photomirex, and chlordecone exposures. Toxicol. Appl. Pharmacol. **61:** 429–440, 1981.
227. CURTIS, L. R., WILLIAMS, W. L., AND MEHENDALE, H. M.: Biliary excretory dysfunction following exposure to photomirex and photomirex/carbon tetrachloride combination. Toxicology **13:** 77–90, 1979.
228. CZECH, M.: Molecular basis of insulin action. Annu. Rev. Biochem. **46:** 359–384, 1977.
229. DANZINGER, R. G., HOFMANN, A. F., SCHOENFIELD, J. L., AND THISTLE, J. L.: Dissolution of cholesterol gallstones by chenodeoxycholic acid. N. Engl. J. Med. **286:** 1–8, 1972.
230. DAVIS, D. R., AND YEARY, R. A.: Interaction of bilirubin and indocyanine green with the binding and conjugation of sulfobromophthalein by rat liver cytosol proteins. Res. Commun. Chem. Pathol. Pharmacol. **27:** 373–388, 1980.
231. DAVIS, M. E., BERNDT, W. O., AND MEHENDALE, H. M.: Alterations of xenobiotic excretory function induced by potassium dichromate or carbon tetrachloride pretreatment. J. Toxicol. Environ. Health **6:** 455–465, 1980.
232. DAVIS, R. A., ENGELHORN, S. C., PANGBURN, S. H., WEINSTEIN, D. B., AND STEINBERG, D.: Very low density lipoprotein synthesis and secretion by cultured rat hepatocytes. J. Biol. Chem. **254:** 2010–2016, 1979.
233. DAVIS, R. A., KERN, F., SHOWALTER, R., SUTHERLAND, I., SINENSKY, M., AND SIMON, F. R.: Alterations of hepatic Na^+, K^+-ATPase and bile flow by estrogen: Effects on liver surface membrane lipid structure and function. Proc. Natl. Acad. Sci. U.S.A. **75:** 4130–4134, 1978.
234. DECKER, C. F., BYERRUM, R. U., AND HOPPERT, C. A.: A study of the distribution and retention of Cd-115 in the albino rat. Arch. Biochem. Biophys. **66:** 140–145, 1957.
235. DELACROIX, D. L., DENEF, A. M., ACOSTA, G. A., MONTGOMERY, P. C., AND VAERMAN, J. P.: Immunoglobulins in rabbit hepatic bile: Selective secretion of IgA and IgM and active plasma-to-bile transfer of polymeric IgA. Scand. J. Immunol. **16:** 343–350, 1982.
236. DELAMIRANDE, E., AND PLAA, G. L.: Role of manganese, bilirubin and sulfobromophthalein in manganese-bilirubin cholestasis in rats. Proc. Soc. Exp. Biol. Med. **158:** 283–287, 1978.
237. DELAMIRANDE, E., AND PLAA, G. L.: Bilirubin excretion pattern in manganese-bilirubin cholestasis. Arch. Int. Pharmacodyn. Ther. **239:** 24–35, 1979.
238. DELAMIRANDE, E., AND PLAA, G. L.: Dose and time relationships in manganese-bilirubin cholestasis. Toxicol. Appl. Pharmacol. **49:** 257–263, 1979.
239. DELAMIRANDE, E., AND PLAA, G. L.: 1,3-Butanediol pretreatment on the cholestasis induced in rats by manganese-bilirubin combination, taurolithocholic acid, or α-naphthylisothiocyanate. Toxicol. Appl. Pharmacol. **59:** 467–475, 1981.
240. DELAMIRANDE, E., TUCHWEBER, B., AND PLAA, G. L.: Hepatocellular membrane alteration as a possible cause of manganese-bilirubin-induced cholestasis. Biochem. Pharmacol. **30:** 2305–2312, 1981.
241. DEMATTEIS, F.: Loss of microsomal components in drug-induced liver damage, in cholestasis and after administration of chemicals which stimulate heme catabolism. Pharm. Ther. A. **2:** 693–725, 1978.
242. DESAIAH, D., HO, I. K., AND MEHENDALE, H. M.: Effects of Kepone and mirex on mitochondrial Mg^{2+}-ATPase activity in rat liver. Toxicol. Appl. Pharmacol. **39:** 219–228, 1977.
243. DESJEUX, J., ERLINGER, S., ET DUMONT, M.: Metabolisme et influence sur la secretion biliare du dehydrocholate chez le chien. Biol. Gastroenterol. **6:** 9–18, 1973.
244. DESMET, V. J.: Morphologic and histochemical aspects of cholestasis. *In* Progress in Liver Diseases, ed. by Grune & Stratton, New York, 1972.
245. DESPOPOULOS, A.: Renal and hepatic transport of food dyes. J. Pharmacol. Exp. Ther. **163:** 222–228, 1968.
246. DESPOPOULOS, A.: Congruence of renal and hepatic excretory functions: Sulfonic acid dyes. Am. J. Physiol. **220:** 1755–1758, 1971.
247. DEWITT, E. H., AND LACK, L.: Effects of sulfation patterns on intestinal transport of bile salt sulfate esters. Am. J. Physiol. **238:** G34–G39, 1980.

248. DeWolf-Peeters, C., DeVos, R., and Desmet, V.: Histochemical changes in rat kidney after bile duct obstruction. Beltr. Pathol. **145:** 315–324, 1972.
249. Dhumeaux, D., Berthelot, P., and Javitt, N. B.: Dibromsulfphalein (DBSP) estimation of hepatic transport function in man. Eur. J. Clin. Invest. **4:** 181–185, 1974.
250. Dhumeaux, D., Berthelot, P., Preaux, A.-M., Erlinger, S., and Fauvert, R.: A critical study of the concept of maximal biliary transport of sulfobromophthalein (BSP) in the Wistar rat. Rev. Eur. Etud. Clin. Biol. **15:** 279–286, 1970.
251. Dhumeaux, D., Erlinger, S., Benhamou, J.-P., and Fauvert, R.: Effects of rose bengal on bile secretion in the rabbit: Inhibition of a bile salt-independent fraction. Gut **11:** 134–140, 1970.
252. Dickinson, R. G., Harland, R. C., Ilias, A. M., Rodgers, R. M., Kaufman, S. N., Lynn, R. K., and Gerber, N.: Disposition of valproic acid in the rat: Dose dependent metabolism, distribution, enterohepatic recirculation and choleretic effect. J. Pharmacol. Exp. Ther. **211:** 583–595, 1979.
253. Dickinson, R. G., Taylor, S. M., Kaufman, S. N., Rodgers, R. M., Lynn, R. K., Gerber, N., and Baughman, W. L.: Nonlinear elimination and choleretic effect of valproic acid in the monkey. J. Pharmacol. Exp. Ther. **213:** 38–48, 1980.
254. Dietschy, J. M.: Recent developments in solute and water transport across the gall bladder epithelium. Gastroenterology **50:** 692–707, 1966.
255. Dietschy, J. M.: Mechanisms for the intestinal absorption of bile acids. J. Lipid Res. **9:** 297–309, 1968.
256. Dillon, L., Kok, E., Wachtel, N., and Javitt, N.: Hepatic bile formation: Modification of concepts of canalicular water flow. Gastroenterology **75:** 961, 1978.
257. Dive, Ch., and Heremans, J. F.: Nature and origin of the proteins of bile. I. A comparative analysis of serum and bile proteins in man. Eur. J. Clin. Invest. **4:** 235–239, 1974.
258. Dive, Ch., Nadalini, R. A., Vaerman, J.-P., and Heremans, J. F.: Origin and nature of the proteins of bile. II. A comparative analysis of serum, hepatic lymph and bile proteins in the dog. Eur. J. Clin. Invest. **4:** 241–246, 1974.
259. Done, A. K.: Developmental pharmacology. Clin. Pharm. Ther. **5:** 432–479, 1964.
260. Dowling, R. H.: The enterohepatic circulation. Gastroenterology **62:** 122–140, 1972.
261. Dowling, R. H., Mack, E., Picott, J., Berger, J., and Small, D. M.: Experimental model for the study of the enterohepatic circulation of bile in rhesus monkeys. J. Lab. Clin. Med. **72:** 169–176, 1968.
262. Dowling, R. H., Mack, E., and Small, D. M.: Biliary lipid secretion and bile composition after acute and chronic interruption of the enterohepatic circulation in the rhesus monkey. IV. Primate biliary physiology. J. Clin. Invest. **50:** 1917–1926, 1971.
263. Drew, R., and Priestly, B. G.: Microsomal drug metabolism during α-naphthylisothiocyanate-induced cholestasis. Toxicol. Appl. Pharmacol. **35:** 491–499, 1976.
264. Drew, R., and Priestly, B. G.: Choleretic and cholestatic effects of infused bile salts in the rat. Experientia (Basel) **35:** 809–810, 1979.
265. Drew, R., and Priestly, B. G.: Effect of chlorpromazine and erythromycin on bile salt-induced cholestasis in the rat. Pharmacology **18:** 202–209, 1979.
266. Drochmans, P., Wanson, J.-C., and Mosselmans, R.: Isolation and subfractionation on Ficoll gradients of adult rat hepatocytes: Size, morphology, and biochemical characteristics of cell fractions. J. Cell Biol. **66:** 1–22, 1975.
267. Duane, W. C., Gilberstadt, M. L., and Wiegand, D. M.: Diurnal rhythms of bile acid production in the rat. Am. J. Physiol. **236:** R175–R179, 1979.
268. Dubin, M., Maurice, M., Feldmann, G., and Erlinger, S.: Phalloidin-induced cholestasis in the rat: Relation to changes in microfilaments. Gastroenterology **75:** 450–455, 1978.
269. Dubin, M., Maurice, M., Feldmann, G., and Erlinger, S.: Influence of colchicine and phalloidin on bile secretion and hepatic ultrastructure in the rat. Gastroenterology **79:** 646–654, 1980.
270. Duggan, D. E.: Sulindac: Therapeutic implications of the prodrug/pharmacophore equilibrium. Drug Metab. Rev. **12:** 325–337, 1981.
271. Duggan, D. E., and Kwan, K. C.: Enterohepatic recirculation of drugs as a determinant of therapeutic ratio. Drug Metab. Rev. **9:** 21–41, 1979.
272. Dujovne, C. A.: Liver cell culture toxicity and surfactant potency of erythromycin derivatives. Toxicol. Appl. Pharmacol. **32:** 11–20, 1975.
273. Dujovne, C. A., Levy, R., and Zimmerman, H. J.: Hepatotoxicity of phenothiazines in vitro as measured by loss of aminotransferases to surrounding media. Proc. Soc. Exp. Biol. Med. **128:** 561–563, 1968.
274. Dujovne, C. A., and Salhab, A. S.: Erythromycin estolate vs. erythromycin base, surface excess properties and surface scanning changes in isolated liver cell systems. Pharmacology **20:** 285–291, 1980.
275. Dujovne, C. A., and Shoeman, D. W.: Human bile excretion and tissue culture of a hepatotoxic laxative preparation. Clin. Pharmacol. Ther. **13:** 602–608, 1972.
276. Dumont, M., and Erlinger, S.: Influence of hydrocortisone on bile formation in the rat. Biol. Gastroenterol. (Paris) **6:** 197–203, 1973.
277. Dumont, M., Erlinger, S., and Uchman, S.: Hypercholeresis induced by ursodeoxycholic acid and 7-ketolithocholic acid in the rat: Possible role of bicarbonate transport. Gastroenterology **79:** 82–89, 1980.
278. Dunkerley, R., Johnson, R., Schenker, S., and Wilkinson, G. R.: Gastric and biliary excretion of meperidine in man. Clin. Pharmacol. Ther. **20:** 546–551, 1976.
279. Dunn, W. A., Hubbard, A. L., and Aronson, N. N., Jr.: Low temperature selectivity inhibits fusion between pinocyte vesicles and lysosomes during heterophagy of ^{125}I-asialofetuin by the perfused liver. J. Biol. Chem. **255:** 5971–5978, 1980.
280. Dutton, G. J., and Burchell, B.: Newer aspects of glucuronidation. Prog. Drug Metab. **2:** 1–70, 1977.
281. Duvaldestin, P., Mahu, J.-L., Metreau, J.-M., Arondel, J., Preaux, A.-M., and Berthelot, P.: Possible role of a defect in hepatic bilirubin glucuronidation in the initiation of cholesterol gallstones. Gut **21:** 650–655, 1980.
282. Dyck, W. P., and Janowitz, H. D.: Effect of glucagon on hepatic bile secretion in man. Gastroenterology **60:** 400–404, 1971.
283. Eakins, M. N.: Bile secretion and cholestasis. *In* Biochemical Mechanism of Liver Injury, ed. by T. F. Slater, pp. 559–590, Academic Press, New York, 1978.
284. Eaton, D. L., and Klaassen, C. D.: Carrier-mediated transport of ouabain in isolated hepatocytes. J. Pharmacol. Exp. Ther. **205:** 480–488, 1978.
285. Eaton, D. L., and Klaassen, C. D.: Carrier-mediated transport of the organic cation procaine amide ethobromide by isolated rat liver parenchymal cells. J. Pharmacol. Exp. Ther. **206:** 595–606, 1978.
286. Eaton, D. L., and Klaassen, C. D.: Effects of microsomal enzyme inducers on carrier-mediated transport systems in isolated rat hepatocytes. J. Pharmacol. Exp. Ther. **208:** 381–385, 1979.
287. Eaton, D. L., and Klaassen, C. D.: Effects of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin, Kepone and polybrominated biphenyls on transport systems in isolated rat hepatocytes. Toxicol. Appl. Pharmacol. **51:** 137–144, 1979.
288. Eaton, D. L., Stacey, N. H., Wong, K.-L., and Klaassen, C. D.: Dose-response effects of various metal ions on rat liver metallothionein, glutathione, heme oxygenase, and cytochrome P-450. Toxicol. Appl. Pharmacol. **55:** 393–402, 1980.
289. Eberle, D., Clarke, R., and Kaplowitz, N.: Rapid oxidation in vitro of endogenous and exogenous glutathione in bile of rats. J. Biol. Chem. **266:** 2115–2117, 1981.
290. Eckel, J., Rao, G. S., Rao, M. L., and Breuer, H.: Uptake of L-triiodothyronine by isolated rat liver cells. Biochem. J. **182:** 473–491, 1979.
291. Eckhardt, E. T., and Plaa, G. L.: Role of biotransformation, biliary excretion and circulatory changes in chlorpromazine-induced sulfobromophthalein retention. J. Pharmacol. Exp. Ther. **139:** 383–389, 1963.
292. Edmondson, J. W., Lumeng, L., and Li, T.-K.: Comparative studies of alanine and α-aminoisobutyric acid uptake by freshly isolated rat liver cells. J. Biol. Chem. **254:** 1653–1658, 1979.
293. Ehrnebo, M., Boreus, L., and Lonroth, U.: Bioavailability and first-pass metabolism of oral pentazocine in man. Clin. Pharmacol. Ther. **22:** 888–892, 1977.
294. Einarsson, K., Grundy, S. M., and Hardison, W. G. M.: Enterohepatic circulation rates of cholic acid and chenodeoxycholic acid in man. Gut **20:** 1078–1082, 1979.
295. El-Hawari, A. M., and Plaa, G. L.: Effects of diazepam on the biliary excretion of diphenylhydantoin in the rat. J. Pharmacol. Exp. Ther. **201:** 14–25, 1977.
296. El-Hawari, A. M., and Plaa, G. L.: Role of the enterohepatic circulation in the elimination of phenytoin in the rat. Drug Metab. Dispos. **6:** 59–69, 1978.
297. Elias, E., Hruban, Z., Wade, J., and Boyer, J. L.: Phalloidin-induced cholestasis: A microfilament-mediated change in junctional complex permeability. Proc. Natl. Acad. Sci. U.S.A. **77:** 2229–2233, 1980.
298. Elinder, C. G., and Pannone, M.: Biliary excretion of cadmium. Environ. Health Perspect. **28:** 123–126, 1979.
299. Engelking, L. R., and Gronwall, R.: Effects of fasting on hepatic bile acid clearance. Proc. Soc. Exp. Biol. Med. **161:** 123–127, 1979.
300. Engelking, L. R., Gronwall, R., and Anwer, M. S.: Effect of bile acid on hepatic excretion and storage of bilirubin in ponies. Am. J. Vet. Res. **37:** 47–50, 1976.
301. Engelking, L. R., Gronwall, R., and Anwer, M. S.: Effect of dehydrocholic, chenodeoxycholic, and taurocholic acids on the excretion of bilirubin. Am. J. Vet. Res. **41:** 355–361, 1980.
302. Enriquez de Salamanca, R., Ladero, J. M., Catalan, T., Mas, V., Rico, R., and Olmos, A.: Hepatic metabolism of bromosulphthalein in Porphyria Cutanea Tarda. Int. J. Biochem. **12:** 855–859, 1980.
303. Eriksson, G., and Strath, D.: Decreased UDP-glucuronic acid in rat liver after ether narcosis. FEBS Lett. **124:** 39–42, 1981.
304. Eriksson, H.: Absorption and enterohepatic circulation of neutral steroids in the rat. Eur. J. Biochem. **19:** 416–423, 1971.
305. Erlinger, S.: The mechanisms of choleresis. Helv. Med. Acta **37:** 153–160, 1973.
306. Erlinger, S.: Hepatocyte bile secretion: Current views and controversies. Hepatology **1:** 352–359, 1981.

307. ERLINGER, S.: Secretion of bile. *In* Disease of the Liver, 5th ed., ed. by L. Schiff and E. R. Schiff, pp. 93–118, J. B. Lippincott, Philadelphia, 1982.
308. ERLINGER, S.: Does Na^+-K^+-ATPase have any role in bile secretion? Am. J. Physiol. **243:** G243–G247, 1982.
309. ERLINGER, S., AND DHUMEAUX, D.: Mechanisms and control of secretion of bile water and electrolytes. Gastroenterology **66:** 281–304, 1974.
310. ERLINGER, S., DHUMEAUX, D., AND BENHAMOU, J.-P.: Effect on bile formation of inhibitors of sodium transport. Nature (Lond.) **223:** 1276–1277, 1969.
311. ERLINGER, S., DHUMEAUX, D. P., BERTHELOT, P., AND DUMONT, M.: Effect of inhibitors of sodium transport on bile formation in the rabbit. Am. J. Physiol. **219:** 416–422, 1970.
312. ERLINGER, S., DUBIN, M., MAURICE, M., AND FELDMAN, N. G.: Modification of bile secretion induced by phalloidin and colchicine in the rat. *In* The Liver. Quantitative Aspects of Structure and Function, ed. by R. Preisig and J. Bircher, pp. 192–196, Editio Cantor, Aulendorf, 1978.
313. ERLINGER, S., AND DUMONT, M.: Influence of canalicular bile flow on BSP transport maximum in bile in the dog. *In* The Liver. Quantitative Aspects of Structure and Function, ed. by G. Paumgartner and R. Preisig, pp. 306–314, Karger, Basel, 1973.
314. ERTTMANN, R. R., AND DAMM, K. H.: Probenecid-induced effects on bile flow and biliary excretion of ^{3}H-ouabain. Arch. Int. Pharmacodyn. Ther. **223:** 96–106, 1976.
315. EVANS, G. W.: Copper homeostasis in the mammalian system. Physiol. Rev. **53:** 535–570, 1973.
316. EVANS, H., KREMMER, T., AND CULVENOR, J. G.: Role of membrane in bile formation. Comparison of the composition of bile and a liver bile-canalicular plasma membrane subfraction. Biochem. J. **154:** 589–595, 1976.
317. EVANS, W. H.: Fractionation of liver plasma membranes prepared by zonal centrifugation. Biochem. J. **116:** 833–842, 1970.
318. EVANS, W. H.: Membrane traffic at the hepatocyte's sinusoidal and canalicular surface domains. Hepatology **1:** 452–457, 1981.
319. EVERSON, G. T., BRAVERMAN, D. Z., JOHNSON, M. L., AND KERN, F., JR.: A critical evaluation of real-time ultrasonography for the study of gallbladder volume and contraction. Gastroenterology **79:** 40–46, 1980.
320. FAILLA, M. L., AND COUSINS, R. J.: Zinc uptake by isolated rat liver parenchymal cells. Biochim. Biophys. Acta **538:** 435–444, 1978.
321. FAILLA, M. L., AND COUSINS, R. J.: Zinc accumulation and metabolism in primary cultures of adult rat liver cells. Biochim. Biophys. Acta **543:** 293–304, 1978.
322. FAILLA, M. L., COUSINS, R. J., AND MASCENIK, M. J.: Cadmium accumulation and metabolism by rat liver parenchymal cells in primary monolayer culture. Biochim. Biophys. Acta **583:** 63–72, 1979.
323. FARAH, A.: On the elimination of G-strophanthin by the rat. J. Pharmacol. Exp. Ther. **86:** 248–257, 1946.
324. FARBER, J. L.: Reactions of the liver to injury: Necrosis. *In* Toxic Injury of the Liver, ed. by E. Farber and M. M. Fisher, pp. 215–241, Marcel Dekker, New York, 1979.
325. FEDOROWSKI, T., SALEN, G., COLALLILO, A., TINT, G. S., MOSBACH, E. H., AND HALL, J. C.: Metabolism of ursodeoxycholic acid in man. Gastroenterology **73:** 1131–1137, 1977.
326. FEDOROWSKI, T., SALEN, G., ZAKI, G., SHEFER, S., AND MOSBACH, E. H.: Comparative effects of ursodeoxycholic acid and chenodeoxycholic acid in the rhesus monkey. Gastroenterology **74:** 75–81, 1978.
327. FEELY, J., WILKINSON, G., AND WOOD, A. J.: Reduction of liver blood flow and propranolol metabolism by cimetidine. N. Engl. J. Med. **304:** 692–695, 1981.
328. FEHLMANN, M., LECAM, A., AND FREYCHET, P.: Insulin and glucagon stimulation of amino acid transport in isolated rat hepatocytes. J. Biol. Chem. **254:** 10431–10437, 1979.
329. FELD, G. K., LOEB, P. M., BERK, R. N., AND WHEELER, H. O.: The choleretic effect of iodipamide. J. Clin. Invest. **55:** 528–535, 1975.
330. FELSHER, B. F.: Effect of changes in dietary components on the serum bilirubin in Gilbert's syndrome. Am. J. Clin. Nutr. **29:** 705–709, 1976.
331. FELSHER, B. F., AND CARPIO, N. M.: Caloric intake and unconjugated hyperbilirubinemia. Gastroenterology **69:** 42–47, 1975.
332. FELSHER, B. F., AND CARPIO, N. M.: Chronic persistent hepatitis and unconjugated hyperbilirubinemia. Gastroenterology **76:** 248–252, 1979.
333. FELSHER, B. F., CARPIO, N. M., AND VAN COUVERING, K.: Effect of fasting and phenobarbital on hepatic UDP-glucuronic acid formation in the rat. J. Lab. Clin. Med. **93:** 414–427, 1979.
334. FELSHER, B. F., RICKARD, D., AND REDEKER, A. G.: The reciprocal relation between caloric intake and the degree of hyperbilirubinemia in Gilbert's syndrome. N. Engl. J. Med. **283:** 170–172, 1970.
335. FEVERY, J., VAN DE VIJVER, M., MICHIELS, R., AND HEIRWEGH, K. P. M.: Comparison in different species of biliary bilirubin-IXα-conjugates with the activities of hepatic and renal bilirubin-IXα-uridine-diphosphate glycosyltransferase. Biochem. J. **164:** 737–746, 1977.
336. FISCHER, A.: Dynamics of the circulation in the liver. *In* The Liver, ed. by C. H. Rouiller, vol. I, pp. 329–371, Academic Press, New York, 1963.
337. FISCHER, E., BARTH, A., KLINGER, W., GREGUS, Z., AND VARGA, F.: Choleretic potencies of some bile acids and their effect on biliary excretion of eosine in the rat. Acta Biol. Med. Ger. **39:** 711–715, 1980.
338. FISCHER, E., BARTH, A., VARGA, F., AND KLINGER, W.: Age dependence of hepatic transport in control and phenobarbital-pretreated rats. Life Sci. **24:** 557–562, 1979.
339. FISCHER, E., AND GREGUS, Z.: Development and regression of the hepatic microsomal enzyme induction and stimulation of biliary excretion produced by phenobarbital in rats. Arch. Int. Pharmacodyn. Ther. **247:** 190–197, 1980.
340. FISCHER, E., GREGUS, Z., AND GOGL, A.: Hepatic transport of sulphobromphthalein and sulphobromphthalein-glutathione conjugate in control and phenobarbital-pretreated rats. Acta Physiol. Acad. Sci. Hung. **51:** 61–66, 1978.
341. FISCHER, E., GREGUS, Z., AND VARGA, F.: Effects of barbiturates on the hepatic cytochrome P-450 dependent enzyme system and biliary excretion of exogenous organic anions in rats. Digestion **20:** 115–120, 1980.
342. FISCHER, E., AND VARGA, F.: Hepatic transport of iodipamide in various animal species. Acta Physiol. Acad. Sci. Hung. **38:** 135–142, 1970.
343. FISCHER, E., AND VARGA, F.: Hepatic storage and biliary excretion of rose bengal in the rat. Acta Physiol. Acad. Sci. Hung. **54:** 89–94, 1979.
344. FISCHER, E., VARGA, F., GREGUS, Z., AND GOGL, A.: Bile flow and biliary excretion rate of some organic anions in phenobarbital-pretreated rats. Digestion **17:** 211–220, 1978.
345. FISCHER, L. J., AND MILLBURN, P.: Stilboestrol transport and glucuronide formation in everted sacs of rat intestine. J. Pharmacol. Exp. Ther. **175:** 267–275, 1970.
346. FISHER, M. M., MAGNUSSON, R., AND MIYAI, K.: Bile acid metabolism in mammals. I. Bile acid-induced intrahepatic cholestasis. Lab. Invest. **21:** 88–91, 1971.
347. FISHER, M. M., NAGY, B., BAZIN, H., AND UNDERDOWN, B. J.: Biliary transport of IgA: Role of secretory component. Proc. Natl. Acad. Sci. U.S.A. **76:** 2008–2012, 1979.
348. FLEISCHNER, G., ROBBINS, J., AND ARIAS, I. M.: Immunological studies of Y protein: A major cytoplasmic organic anion-binding protein in rat liver. J. Clin. Invest. **51:** 677–684, 1972.
349. FOLDES, O., LANGER, P., STRAUSSOVA, K., BROZMANOVA, H., AND GSCHWENDTOVA, K.: Direct quantitative estimation of several iodothyronines in rat bile by radioimmunoassay and basal data on their biliary excretion. Biochim. Biophys. Acta **716:** 383–390, 1982.
350. FORKER, E. L.: Two sites of bile formation as determined by mannitol and erythritol clearance in the guinea pig. J. Clin. Invest. **46:** 1189–1195, 1967.
351. FORKER, E. L.: Bile formation in guinea pigs: Analysis with inert solutes of graded molecular radius. Am. J. Physiol. **215:** 56–62, 1968.
352. FORKER, E. L.: The effect of estrogen on bile formation in the rat. J. Clin. Invest. **48:** 654–663, 1969.
353. FORKER, E. L.: Hepatocellular uptake of insulin, sucrose and mannitol in rats. Am. J. Physiol. **219:** 1568–1573, 1970.
354. FORKER, E. L.: Mechanisms of hepatic bile formation. Annu. Rev. Physiol. **39:** 323–347, 1977.
355. FORKER, E. L., AND GIBSON, G.: Interaction between sulfobromophthalein (BSP) and taurocholate. The kinetics of transport from liver cells to bile in rats. *In* The Liver. Quantitative Aspects of Structure and Function, ed. by G. Paumgartner and R. Preisig, pp. 326–336, Karger, Basel, 1973.
356. FORKER, E. L., HICKLIN, T., AND SORNSON, H.: The clearance of mannitol and erythritol in rat bile. Proc. Soc. Exp. Biol. Med. **126:** 115–119, 1967.
357. FORKER, E. L., AND LUXON, B. A.: Albumin helps mediate removal of taurocholate by rat liver. J. Clin. Invest. **67:** 1517–1522, 1981.
358. FORKER, E. L., LUXON, B. A., SNELL, M., AND SHURMANTINE, W. O.: Effect of albumin binding on the hepatic transport of rose bengal: Surface-mediated dissociation of limited capacity. J. Pharmacol. Exp. Ther. **223:** 342–347, 1982.
359. FORSSMANN, W. G., AND ITO, S.: Hepatocyte innervation in primates. J. Cell Biol. **74:** 299–313, 1977.
360. FOUCHEREAU-PERON, M., BROER, Y., AND ROSSELIN, G.: Growth hormone and insulin binding to isolated hepatocytes in the genetically dwarf mouse. Biochim. Biophys. Acta **631:** 451–462, 1980.
361. FRAZIER, J. M., AND KINGSLEY, B. S.: Kinetics of cadmium transport in the isolated perfused rat liver. Toxicol. Appl. Pharmacol. **38:** 583–593, 1976.
362. FRAZIER, J. M., AND PUGLESE, J.: Dose dependence of cadmium kinetics in the rat liver following intravenous injection. Toxicol. Appl. Pharmacol. **43:** 461–474, 1978.
363. FRENCH, S. W., AND DAVIES, P. L.: Ultrastructural localization of actin-like filaments in rat hepatocytes. Gastroenterology **68:** 765–774, 1975.
364. FREZZA, M., TIRIBELLI, C., PANFILI, E., AND SANDRI, G.: Evidence for the existence of a carrier for bromosulphophthalein in the liver cell plasma membrane. FEBS Lett. **38:** 125–128, 1974.
365. FRIEND, D. S., AND GILULA, N. B.: Variations in tight and gap junctions in mammalian tissues. J. Cell Biol. **53:** 758–776, 1972.
366. FRIMMER, M., PETZINGER, E., RUFEGER, U., AND VEIL, L. B.: The role of bile acids in phalloidin poisoning. Naunyn-Schmiedeberg's Arch. Pharmacol. **301:** 145–147, 1977.
367. FRITZ, M. E., AND BROOKS, F. P.: Control of bile flow in the cholecystectomized dog. Am. J. Physiol. **204:** 825–828, 1963.
368. FROMMEL, D., AND RACHMAN, F.: Receptor for the Fc portion of IgG on

the plasma membrane of the hepatocyte. Ann. Immunol. (Paris) **130C:** 553–560, 1979.
369. FROMMER, D. J.: Biliary copper excretion in man and the rat. Digestion **15:** 390–396, 1977.
370. FROMTER, E., AND DIAMOND, J.: Route of passive ion permeation in epithelia. Nature (Lond.) New Biol. **235:** 9–13, 1972.
371. FUJIMOTO, J. M.: Some in vivo methods for studying sites of toxicant action in relation to bile formation. *In* Toxicology of the Liver, ed. by G. Plaa and W. Hewitt, pp. 121–145, Raven Press, New York, 1982.
372. FUHRMAN-LANE, C., ERWIN, C., FUJIMOTO, J., AND DIBBEN, M. J.: Altered hepatobiliary permeability induced by amanita phalloides in the rat and the protective role of bile duct ligation. Toxicol. Appl. Pharmacol. **58:** 370–378, 1981.
373. FUHRMAN-LANE, C., AND FUJIMOTO, J. M.: Effects of trans-stilbene oxide treatment on biliary excretion of xenobiotics in the rat. Drug Metab. Dispos. **10:** 505–509, 1982.
374. GABBIANI, G., MONTESANO, R., TUCHWEBER, B., SALAS, M., AND ORCI, L.: Phalloidin-induced hyperplasia of actin filaments in rat hepatocytes. Lab. Invest. **33:** 562–569, 1975.
375. GABBIANI, G., AND RYAN, G. B.: Development of a contractile apparatus in epithelial cells during epidermal and liver regeneration. J. Subm. Cytol. **6:** 143–157, 1974.
376. GALLAGHER, T. F., JR., MUELLER, M. N., AND KAPPAS, A.: Estrogen pharmacology. IV. Studies on the structural basis for estrogen-induced impairment of liver function. Medicine **45:** 471–479, 1966.
377. GALVIN, M. J., AND LEFER, A. M.: Hepatic blood flow in acute myocardial ischemia. Experientia (Basel) **35:** 1602–1603, 1979.
378. GAMAGEE, A.: A Text-Book of the Physiological Chemistry of the Animal Body, vol. II, p. 267, Macmillan and Co., London, 1893.
379. GANDOLFI, A. J., AND BUHLER, D. R.: Biliary metabolites and enterohepatic circulation of hexachlorophene in the rat. Xenobiotica **4:** 693–704, 1974.
380. GARDNER, B., MASUR, R., PATTI, J., AND OSTROWITZ, A.: Effect of taurocholic acid and BSP on conjugation patterns and suspension stability of human and rat bile. Am. J. Surg. **125:** 204–210, 1973.
381. GARTNER, L. M., AND ARIAS, I. M.: The transfer of bilirubin from blood to bile in the neonatal guinea pig. Pediat. Res. **3:** 171–180, 1969.
382. GARTNER, U., STOCKERT, R. J., LEVINE, W. G., AND WOLKOFF, A. M.: Effect of nafenopin on the uptake of bilirubin and sulfobromophthalein by isolated perfused rat liver. Gastroenterology **83:** 1163–1169, 1982.
383. GEIST, R. E., AND JONES, R. S.: Effect of selective and truncal vagotomy on insulin-stimulated bile secretion in dogs. Gastroenterology **60:** 566–571, 1971.
384. GENTILINI, P., TEODORI, U., GORINI, S., AND POPPER, H.: Intrahepatic Cholestasis, Raven Press, New York, 1975.
385. GIBALDI, M., AND FELDMAN, S.: Route of administration and drug metabolism. Eur. J. Pharmacol. **19:** 323–329, 1972.
386. GIBALDI, M., AND PERRIER, D.: Route of administration and drug disposition. Drug Metab. Rev. **3:** 185–199, 1974.
387. GIBSON, G. E., AND FORKER, E. L.: Canalicular bile flow and bromosulfophthalein transport maximum: The effect of a bile salt-independent choleretic SC-2644. Gastroenterology **66:** 1046–1053, 1974.
388. GIEBISH, G., AND MALNIC, G.: Studies on the mechanism of tubular acidification. Physiologist **19:** 511–524, 1976.
389. GILLETTE, J. R., AND PANG, S.: Theoretic aspects of pharmacokinetic drug interactions. Clin. Pharmacol. Ther. **22:** 623–639, 1977.
390. GILMORE, I. T., BARNHART, J. L., HOFMANN, A. F., AND ERLINGER, S.: Effects of individual taurine-conjugated bile acids on biliary lipid secretion and sucrose clearance in the unanesthetized dog. Am. J. Physiol. **242:** G40–G46, 1982.
391. GIRKIN, R., BALDOCK, G. A., CHASSEAUD, L. F., HUMPEL, M., HAWKINS, D. R., AND MAYO, B. C.: The absorption, distribution and excretion of [^{14}C]lormetazepam in dogs, rabbits, rats and rhesus monkeys. Xenobiotica **10:** 401–411, 1980.
392. GLASINOVIC, J.-C., DUMONT, M., DUVAL, M., AND ERLINGER, S.: Hepatocellular uptake of erythritol and mannitol in the dog. Am. J. Physiol. **229:** 1455–1460, 1975.
393. GLASINOVIC, J.-C., DUMONT, M., DUVAL, M., AND ERLINGER, S.: Hepatocellular uptake of taurocholate in the dog. J. Clin. Invest. **55:** 419–426, 1975.
394. GODFREY, P. P., WARNER, M. J., AND COLEMAN, R.: Enzymes and proteins in bile. Biochem. J. **196:** 11–16, 1981.
395. GOLDSTEIN, J. A., AND TAUROG, A.: Enhanced biliary excretion of thyroxine glucuronide in rats pretreated with benzpyrene. Biochem. Pharmacol. **17:** 1049–1065, 1968.
396. GOLLAN, J. L., AND DELLER, D. J.: Studies on the nature and excretion of biliary copper in man. Clin. Sci. Mol. Med. **44:** 9–15, 1973.
397. GOLLAN, J. L., HUANG, S. N., BILLING, B. H., AND SHERLOCK, S.: Prolonged survival in three brothers with severe type 2 Crigler-Najjar syndrome. Ultrastructural and metabolic studies. Gastroenterology **68:** 1543–1555, 1975.
398. GONZALEZ, M. C., SUTHERLAND, E., AND SIMON, F. R.: Regulation of hepatic transport of bile salts. Effect of protein synthesis inhibition on excretion of bile salts and their binding to liver surface membrane fractions. J. Clin. Invest. **63:** 684–694, 1979.
399. GORDON, E. R., GORESKY, C. A., CHAN, T. H., AND PERLIN, A. S.: The isolation and characterization of bilirubin diglucuronide, the major bilirubin conjugate in dog and human bile. Biochem. J. **155:** 477–486, 1976.
400. GORESKY, C. A.: Initial distribution and rate of uptake of sulfobromophthalein in the liver. Am. J. Physiol. **207:** 13–26, 1964.
401. GORESKY, C. A.: Uptake in the liver: The nature of the process. Int. Rev. Physiol. **21:** 65–101, 1980.
402. GORESKY, C. A., BACH, G. G., AND NADEAU, B. E.: On the uptake of materials by the intact liver. The transport and net removal of galactose. J. Clin. Invest. **52:** 991–998, 1973.
403. GORESKY, C. A., GORDON, E. R., SHAFFER, E. A., PARE, P., CARASSAVAS, D., AND ARONOFF, A.: Definition of a conjugation dysfunction in Gilbert's syndrome: Studies of the handling of bilirubin loads and of the pattern of bilirubin conjugates secreted in bile. Clin. Sci. Mol. Med. **55:** 63–71, 1978.
404. GORESKY, C. A., HADDAD, H. H., KLUGER, W. S., NADEAU, B. E., AND BACH, G. G.: The enhancement of maximal bilirubin excretion with taurocholate-induced increments in bile flow. Can. J. Physiol. Pharmacol. **52:** 389–403, 1974.
405. GORESKY, C. A., HOLMES, T. H., AND SASS-KORTSAK, A.: The initial uptake of copper by the liver in the dog. Can. J. Physiol. Pharmacol. **46:** 771–784, 1968.
406. GOTZ, R., SCHWARZ, L. R., AND GREIM, H.: Effects of pentachlorophenol and 2,4,6-trichlorophenol on the disposition of sulfobromophthalein and respiration of isolated liver cells. Arch. Toxicol. **44:** 147–155, 1980.
407. GOURLAY, S. J., AND JONES, R. S.: Effect of truncal vagotomy on 2-deoxy-D-glucose and insulin choleresis. Ann. Surg. **176:** 645–648, 1972.
408. GOVINDAN, V. M., FAULSTICH, H., WIELAND, T., AGOSTINI, B., AND HASSELBACH, W.: In vitro effect of phalloidin on a plasma membrane preparation from rat liver. Naturwissenschaften **59:** 521–522, 1972.
409. GRAF, J.: Some aspects of the role of cyclic AMP and calcium in bile formation: Studies in the isolated perfused rat liver. *In* Stimulus-Secretion Coupling in the Gastrointestinal Tract, ed. by R. M. Case and H. Goebell, pp. 305–330, University Park Press, Baltimore, 1976.
410. GRAF, J., KORN, P., AND PETERLIK, M.: Choleretic effects of ouabain and ethacrynic acid in the isolated perfused rat liver. Naunyn-Schmiedeberg's Arch. Pharmacol. **272:** 230–233, 1972.
411. GRAF, J., AND PETERLIK, M.: Mechanism of transport of inorganic ions into bile. *In* The Hepatobiliary System-Fundamental and Pathological Mechanisms, ed. by W. Taylor, pp. 43–58, Plenum, New York, 1975.
412. GRAF, J., AND PETERLIK, M.: Ouabain-mediated sodium uptake and bile formation by isolated perfused rat liver. Am. J. Physiol. **230:** 876–885, 1976.
413. GRAHAM, E. A., COLE, W. H., AND COPHER, G. H.: Cholecystography. The use of sodium tetraiodophenolphthalein. J.A.M.A. **84:** 1175–1177, 1925.
414. GRANT, D. A. W., AND FLEMING, S. C. The biliary excretion of trypsin in rats. Biosci. Rep. **1:** 765–770, 1981.
415. GREENBERG, D. M., AND CAMPBELL, W. W.: Studies in mineral metabolism with the aid of induced radioactive isotopes. IV. Manganese. Proc. Natl. Acad. Sci. U.S.A. **26:** 448–452, 1940.
416. GREENBERG, D. M., COPP, D. H., AND CUTHBERTSON, E. M.: Studies in mineral metabolism with the aid of artificial radioactive isotopes. VII. The distribution and excretion, particularly by way of the bile, of iron, cobalt, and manganese. J. Biol. Chem. **147:** 749–756, 1943.
417. GREENSLADE, D., HAVLER, M. E., HUMPHREY, M. J., JORDAN, B. J., AND RANCE, M. J.: Species differences in the metabolism and excretion of fenclofenac. Xenobiotica **10:** 753–760, 1980.
418. GREENWAY, C. V., AND STARK, R. D.: Hepatic vascular bed. Physiol. Rev. **51:** 23–65, 1971.
419. GREGORY, D. H., VLAHCEVIC, Z. R., PRUGHL, M. F., AND SWELL, L.: Mechanism of secretion of biliary lipids: Role of a microtubular system in hepatocellular transport of biliary lipids in the rat. Gastroenterology **74:** 93–100, 1978.
420. GREGORY, D. H., VLAHCEVIC, Z. R., SCHATZKI, P., AND SWELL, L.: Mechanism of secretion of biliary lipids. I. Role of bile canalicular and microsomal membranes in the synthesis and transport of biliary lecithin and cholesterol. J. Clin. Invest. **55:** 105–114, 1975.
421. GREGUS, Z., BARTH, A., FISCHER, E., ZAUMSEIL, J., KLINGER, W., AND VARGA, F.: Comparison of the effects of cholestyramine and aluminum hydroxide on the biliary bile acid excretion in rats. An experimental model for the depletion of bile acids in bile. Acta Biol. Med. Ger. **39:** 705–709, 1980.
422. GREGUS, Z., AND FISCHER, E.: Effect of sodium taurocholate on hepatic uptake and biliary excretion of organic anions in rats. Arch. Int. Pharmacodyn. Ther. **240:** 180–192, 1979.
423. GREGUS, Z., AND FISCHER, E.: Qualitative differences in the hepatobiliary transport of sulfobromophthalein (BSP) and its glutathione conjugate (BSP-GSH). Acta Med. Acad. Sci. Hung. **37:** 315–320, 1980.
424. GREGUS, Z., FISCHER, E., AND VARGA, F.: Inhibition by bromsulphthalein of the biliary excretion of its glutathione conjugate. Biochem. Pharmacol. **26:** 1951–1952, 1977.
425. GREGUS, Z., FISCHER, E., AND VARGA, F.: Correlation between hepatic transport of cholephilic organic anions and their effect on hepatic

mitochondrial respiration. Acta Med. Acad. Sci. Hung. **36:** 197–202, 1979.
426. GREGUS, Z., FISCHER, E., AND VARGA, F.: Effect of sodium taurocholate on the hepatic transport of bromsulphthalein in rats. Arch. Int. Pharmacodyn. Ther. **238:** 124–133, 1979.
427. GREGUS, Z., FISCHER, E., AND VARGA, F.: Effect of cholestyramine-induced bile acid depletion on the hepatobiliary transport of cholephilic organic anions in rats. Arch. Int. Pharmacodyn. Ther. **245:** 311–322, 1980.
428. GREGUS, Z., AND KLAASSEN, C. D.: Comparison of biliary excretion of organic anions in mice and rats. Toxicol. Appl. Pharmacol. **63:** 13–20, 1982.
429. GREGUS, Z., AND KLAASSEN, C. D.: Role of ligandin as a binding protein and as an enzyme in the biliary excretion of sulfobromophthalein. J. Pharmacol. Exp. Ther. **221:** 242–246, 1982.
430. GREGUS, Z., VARGA, F., AND FISCHER, E.: Effect of bile acids on the biliary excretion of amaranth and the respiration of liver mitochondria. Acta Physiol. Acad. Sci. Hung. **59:** 89–97, 1982.
431. GREGUS, Z., WATKINS, J. B., THOMPSON, T. N., HARVEY, M. J., ROZMAN, K., AND KLAASSEN, C. D.: Hepatic phase I and phase II biotransformation in quail and trout: Comparison to other species commonly used in toxicity testing. Toxicol. Appl. Pharmacol. **67:** 430–441, 1983.
432. GREGUS, Z., WATKINS, J. B., THOMPSON, T. N., AND KLAASSEN, C. D.: Resistance of some phase II biotransformation pathways to hepatotoxins. J. Pharmacol. Exp. Ther. **222:** 471–479, 1982.
433. GREGUS, Z., WATKINS, J. B., THOMPSON, T. N., AND KLAASSEN, C. D.: Depletion of hepatic UDP-glucuronic acid decreases the biliary excretion of drugs. J. Pharmacol. Exp. Ther. **225:** 256–262, 1983.
434. GROHLICH, D., MORLEY, C. G. D., AND BEZKOROVAINY, A.: Some aspects of iron uptake by rat hepatocytes in suspension. Int. J. Biochem. **10:** 797–802, 1979.
435. GROHLICH, D., MORLEY, C. G. D., MILLER, R. J., AND BEZKOROVAINY, A.: Iron incorporation into isolated rat hepatocytes. Biochem. Biophys. Res. Commun. **76:** 682–690, 1977.
436. GROSZMANN, R. J., KOTELANSKI, B., KENDLER, J., AND ZIMMERMAN, H. J.: Effect of sulfobromophthalein and indocyanine green on bile excretion. Proc. Soc. Exp. Biol. Med. **132:** 712–714, 1969.
437. GRUNDIN, R., MOLDEUS, P., ORRENIUS, S., BORG, K. O., SKANBERG, I., AND VON BAHR, C.: The possible role of cytochrome P-450 in the liver "first pass elimination" of a β-receptor blocking drug. Acta Pharmacol. Toxicol. **35:** 242–260, 1974.
438. GRUNDY, S. M., METZGER, A. L., AND ADLER, R. D.: Mechanisms of lithogenic bile formation in American Indian women with cholesterol gallstones. J. Clin. Invest. **51:** 3026–3043, 1972.
439. GUARINO, A. M., AND SCHANKER, L. S.: Biliary excretion of probenecid and its glucuronide. J. Pharmacol. Exp. Ther. **164:** 387–395, 1968.
440. GUMUCIO, J. J., ACCATINO, L., MACHO, A. M., AND CONTRERAS, A.: Effect of phenobarbital on the ethynyl estradiol-induced cholestasis in the rat. Gastroenterology **65:** 651–657, 1973.
441. GUMUCIO, J. J., BALABAUD, C., MILLER, D. L., DEMASON, L. J., APPELMAN, H. D., STOECKER, T. J., AND FRANZBLAU, D.: Bile secretion and liver cell heterogeneity in the rat. J. Lab. Clin. Med. **91:** 350–362, 1978.
442. GUMUCIO, J. J., DEMASON, L. J., MILLER, D. L., KREZOSKI, S. O., AND KEENER, M.: Induction of cytochrome P-450 in a selective subpopulation of hepatocytes. Am. J. Physiol. **234:** C102–C109, 1978.
443. GUMUCIO, J. J., KATZ, M. E., MILLER, D. L., BALABAUD, C. P., GREENFIELD, J. M., AND WAGNER, R. M.: Bile salt transport after selective damage to acinar zone 3 hepatocytes by bromobenzene in the rat. Toxicol. Appl. Pharmacol. **50:** 77–85, 1979.
444. GUMUCIO, J. J., AND MILLER, D. L.: Functional implications of liver cell heterogeneity. Gastroenterology **80:** 393–403, 1981.
445. GUMUCIO, J. J., MILLER, D. L., KRAUSS, M. D., AND ZANOLLI, C. C.: Transport of fluorescent compounds into hepatocytes and the resultant zonal labeling of the hepatic acinus in the rat. Gastroenterology **80:** 639–645, 1981.
446. GUMUCIO, J. J., AND VALDIVIESO, V. D.: Studies on the mechanism of the ethynylestradiol impairment of bile flow and bile salt excretion in the rat. Gastroenterology **61:** 339–344, 1971.
447. GUZELIAN, P., AND BOYER, J. L.: Glucose reabsorption from bile. Evidence for a biliohepatic circulation. J. Clin. Invest. **53:** 526–535, 1974.
448. GUZELIAN, P. S., VRANIAN, G., BOYLAN, J. J., COHN, W. J., AND BLANKE, R. V.: Liver structure and function in patients poisoned with chlordecone (Kepone). Gastroenterology **78:** 206–213, 1980.
449. HABIF, D. V., RANDALL, H. T., AND SOROFF, H. S.: The management of cirrhosis of the liver and ascites with particular reference to the portacaval shunt operation. Surgery **34:** 580–605, 1953.
450. HABIG, W. H., PABST, M. J., FLEISCHNER, G., GATMAITAN, Z., ARIAS, I. M., AND JAKOBY, W. B.: The identity of glutathione S-transferase B with ligandin, a major binding protein of liver. Proc. Natl. Acad. Sci. U.S.A. **71:** 3879–3882, 1974.
451. HABIG, W. H., PABST, M. J., AND JAKOBY, W. B.: Glutathione S-transferases. The first enzymatic step in mercapturic acid formation. J. Biol. Chem. **249:** 7130–7139, 1974.
452. HACKI, W., AND PAUMGARTNER, G.: Determination of the biliary dead space using ^{14}C-taurocholate as a marker. Experientia (Basel) **29:** 1091–1093, 1973.
453. HADDOW, J. E., FISH, C. A., MARSHALL, P. C., AND LESTER, R.: Biliary excretion of mercury enhanced by spironolactone. Gastroenterology **63:** 1053–1058, 1972.
454. HADDOW, J. E., AND LESTER, R.: Biliary copper excretion in the rat is enhanced by spironolactone. Drug Metab. Dispos. **4:** 499–503, 1976.
455. HADDOW, J. E., AND MARSHALL, P.: Increased stool mercury excretion in the rat: The effect of spironolactone. Proc. Soc. Exp. Biol. Med. **140:** 707–709, 1972.
456. HAMADA, N., AND PETERSON, R. E.: Effect of microsomal enzyme inducers on 2,3,7,8-tetrachlorodibenzo-*p*-dioxin-induced depression in the biliary excretion of ouabain in rats. Drug Metab. Dispos. **6:** 456–464, 1978.
457. HANAHAN, D. J., DASKALAKIS, E. G., EDWARDS, T., AND DAUBEN, H. J., JR.: The metabolic pattern of C^{14}-diethylstilbestrol. Endocrinology **53:** 163–170, 1953.
458. HANASONO, G. K., DEREPENTIGNY, L., PRIESTLY, B. G., AND PLAA, G. L.: The effects of oral diazepam pretreatment on the biliary excretion of sulfobromophthalein in rats. Can. J. Physiol. Pharmacol. **54:** 603–612, 1976.
459. HANDSCHUMACHER, R. E., AND COLERIDGE, J.: Hepatic and biliary transport of orotate and its metabolic consequences. Biochem. Pharmacol. **28:** 1977–1981, 1979.
460. HANZON, V.: Liver cell secretion under normal and pathologic conditions studied by fluorescence microscopy on living rats. Acta Physiol. Scand. **28** (suppl. 101): 5–268, 1952.
461. HARDISON, W. G. M., AND APTER, J. T.: Micellar theory of biliary cholesterol excretion. Am. J. Physiol. **222:** 61–67, 1972.
462. HARDISON, W. G. M., HATOFF, D. E., MIYAI, K., AND WEINER, R. G.: Nature of bile acid maximum secretory rate in the rat. Am. J. Physiol. **241:** G337–G343, 1981.
463. HARDISON, W. G. M., AND NORMAN, J. C.: Electrolyte composition of the secretin fraction of bile from the perfused pig liver. Am. J. Physiol. **214:** 758–763, 1968.
464. HARDISON, W. G. M., AND WEINER, R. G.: Taurine transport by rat hepatocytes in primary culture. Biochim. Biophys. Acta **598:** 145–152, 1980.
465. HARDISON, W. G. M., AND WOOD, C. A.: Importance of bicarbonate in bile salt independent fraction of bile flow. Am. J. Physiol. **235:** E158–E164, 1978.
466. HART, L. G., GUARINO, A. M., AND ADAMSON, R. H.: Effects of phenobarbital on biliary excretion of organic acids in male and female rats. Am. J. Physiol. **217:** 46–52, 1969.
467. HART, L. G., AND SCHANKER, L. S.: The chemical forms in which phenol red is secreted into the bile of rats. Proc. Soc. Exp. Biol. Med. **123:** 433–435, 1966.
468. HARTY, R. F., ROSE, R. C., AND NAHRWOLD, D. J.: Stimulation of hepatic bile secretion by dopamine. J. Surg. Res. **17:** 359–363, 1974.
469. HASLEWOOD, G. A. D.: Comparative Biochemistry, vol. 3, ed. by M. Florkin and H. S. Mason, p. 205, Academic Press, New York and London,1962.
470. HASLEWOOD, G. A. D.: Evolution and bile salts. *In* Handbook of Physiology, Section 6: Alimentary Canal, ed. by C. F. Code, pp. 2375–2390, American Physiological Society, Washington, DC, 1968.
471. HAVRDOVA, J., CIKRT, M., AND TICHY, M.: Binding of cadmium and mercury in the rat bile: Studies using gel filtration. Acta Pharmacol. Toxicol. **34:** 246–253, 1974.
472. HEANEY, R. P., AND WHEDON, G. D.: Impairment of hepatic bromsulphalein clearance by two 17-substituted testosterones. J. Lab. Clin. Med. **52:** 169–175, 1958.
473. HEATH, T., CAPLE, I. W., AND REDDING, P. M.: Effect of the enterohepatic circulation of bile salts on the flow of bile and its content of bile salts and lipids in sheep. Q. J. Exp. Physiol. **55:** 93–103, 1970.
474. HEIKEL, T. A. J., AND LATHE, G. H.: The effect of 17α-ethinyl-substituted steroids on adenosine triphosphatases of rat liver plasma membrane. Biochem. J. **118:** 187–189, 1970.
475. HEIKEL, T. A. J., AND LATHE, G. H.: The effect of oral contraceptive steroids on bile secretion and bilirubin Tm in the rats. Br. J. Pharmacol. **38:** 593–601, 1970.
476. HEINEMAN, H. B., SMYTHE, C. M., AND MARKS, P. A.: Effect of hemorrhage on EHBF and renal blood flow in dogs. Am. J. Physiol. **174:** 352–361, 1953.
477. HENDERSON, J. R.: Insulin in body fluids other than blood. Physiol. Rev. **54:** 1–22, 1974.
478. HERTZOG, P. J., BHATHAL, P. S., DORLING, P. R., AND LEPAGE, R. N.: α-Naphthyl-isothiocyanate-induced cholestasis in the rat: Studies of liver plasma membrane enzymes. Pathology **7:** 13–23, 1975.
479. HERZ, R., CUENI, B., BIRCHER, J., AND PAUMGARTNER, G.: The excretory capacity of the isolated rat liver. Naunyn-Schmiedeberg's Arch. Pharmacol. **277:** 297–304, 1973.
480. HEWITT, W. R., AND PLAA, G. L.: Potentiation of carbon tetrachloride-induced hepatotoxicity by 1,3-butanediol. Toxicol. Appl. Pharmacol. **47:** 177–180, 1979.
481. HILES, R. A.: Absorption, distribution and excretion of inorganic tin in rats. Toxicol. Appl. Pharmacol. **27:** 366–379, 1974.
482. HILES, R. A., CAUDILL, D., BIRCH, C. G., AND EICHHOLD, T.: The metabolism and disposition of 3,4,4′-trichlorocarbanilide in the intact and bile

duct-cannulated adult and in the newborn rhesus monkey (M. mulatta). Toxicol. Appl. Pharmacol. 46: 593–606, 1978.
483. HINTON, R. H., MULLOCK, B. M., PEPPARD, J., AND ORLANS, E.: Role of endocytic vesicles in the transport of proteins into bile. Biochem. Soc. Trans. 8: 114, 1980.
484. HIRAI, S., HUSSAIN, A., HADDADIN, M., AND SMITH, R. B.: First-pass metabolism of ethinyl estradiol in dogs and rats. J. Pharm. Sci. 70: 403–406, 1981.
485. HIRATA, E., AND TAKAHASHI, H.: Degradation of methyl mercury glutathione by the pancreatic enzymes in bile. Toxicol. Appl. Pharmacol. 58: 483–491, 1981.
486. HIROM, P. C., HUGHES, R. D., AND MILBURN, P.: The physicochemical factor required for the biliary excretion of organic cations and anions. Biochem. Soc. Trans. 2: 327–330, 1974.
487. HIROM, P. C., MILLBURN, P., AND SMITH, R. L.: Bile and urine as complementary pathways for the excretion of foreign organic compounds. Xenobiotica 6: 55–64, 1976.
488. HIROM, P. C., MILLBURN, P., SMITH, R. L., AND WILLIAMS, R. T.: Species variations in the threshold molecular-weight factor for the biliary excretion of organic anions. Biochem. J. 129: 1071–1077, 1972.
489. HIROM, P. C., MILLBURN, P., SMITH, R. L., AND WILLIAMS, R. T.: Molecular weight and chemical structure as factors in the biliary excretion of sulphonamides in the rat. Xenobiotica 2: 205–214, 1972.
490. HISLOP, I. G.: The absorption and entero-hepatic circulation of bile salts: An historical review. Med. J. Aust. 1: 1223–1226, 1970.
491. HO, K.-J., AND DRUMMOND, J. L.: Circadian rhythm of biliary excretion and its control mechanisms in rats with chronic biliary drainage. Am. J. Physiol. 229: 1427–1437, 1975.
492. HOENIG, V.: Effect of ethinyl estradiol and Triton WR 1339 on bile formation and sulfobromophthalein transport maximum (BSP_{Tm}) in the rat. Pharmacol. Res. Commun. 13: 903–908, 1981.
493. HOENIG, V., AND PREISIG, R.: Organic-anionic choleresis in the dog: Comparative effects of bromsulfalein, ioglycamide and taurocholate. Biomedicine 18: 23–30, 1973.
494. HOENIG, V., AND WERNER, FR.: Effect of perhexiline maleate on bile formation and liver disposition of sulfobromophthalein in the rat. Pharmacol. Res. Commun. 12: 931–936, 1980.
495. HOFFMAN, N. E., ISER, J. H., AND SMALLWOOD, R. A.: Hepatic bile acid transport: effect of conjugation and position of hydroxyl groups. Am. J. Physiol. 229: 298–302, 1975.
496. HOFFMAN, N. E., SEWELL, R. B., AND SMALLWOOD, R. A.: Bile acid structure and biliary lipid secretion. II. A comparison of three hydroxy and two keto bile acids. Am. J. Physiol. 234: E637–E640, 1978.
497. HOFMANN, A. F.: The enterohepatic circulation of bile acids in man. Adv. Intern. Med. 21: 501–534, 1976.
498. HOFMANN, A. F.: The enterohepatic circulation of bile acids in man. *In* Bile Acids. Clinics in Gastroenterology, ed. by G. Paumgartner, vol. 6, pp. 3–24, W. B. Saunders, Philadelphia, 1977.
499. HOFMANN, A. F.: The medical treatment of cholesterol gallstones. Am. J. Med. 69: 4–7, 1980.
500. HOLBOROW, E. J., TRENCHEV, P. S., DORLING, J., AND WEBB, J.: Demonstration of smooth muscle contractile protein antigens in liver and epithelial cells. Ann. N.Y. Acad. Sci. 254: 489–504, 1975.
501. HOLDSWORTH, G., AND COLEMAN, R.: Enzyme profiles of mammalian bile. Biochim. Biophys. Acta 389: 47–50, 1975.
502. HOLM, I., THULIN, L., SAMNEGARD, H., EFENDIC, S., AND TYDEN, G.: Anticholeretic effect of somatostatin in anesthetized dogs. Acta Physiol. Scand. 104: 241–243, 1978.
503. HOLSTI, P.: Experimental cirrhosis of the liver in rabbits induced by gastric instillation of dessicated whole bile. Acta Pathol. Microbiol. Scand. Suppl. 113: 1–67, 1956.
504. HOLSTI, P.: Cirrhosis of the liver induced in rabbits by gastric instillation of 3-monohydroxycholanic acid. Nature (Lond.) 186: 250, 1960.
505. HOPF, U., MEYER ZUM BUSCHENFELDE, K. H., AND DIERICH, M. P.: Demonstration of binding sites for IgG Fc and the third complement component (C3) on isolated hepatocytes. J. Immunol. 117: 639–645, 1976.
506. HOPF, U., SCHAEFER, H. E., HESS, G., AND MEYER ZUM BUSCHENFELDE, K. H.: In vivo uptake of immune complexes by parenchymal and nonparenchymal liver cells in mice. Gastroenterology 80: 250–259, 1981.
507. HORAK, W., GRABNER, G., AND PAUMGARTNER, G.: Inhibition of bile salt-independent bile formation by indocyanine green. Gastroenterology 64: 1005–1012, 1973.
508. HORAK, W., GRABNER, G., AND PAUMGARTNER, G.: Effect of indocyanine green on bile flow and bile salt excretion. Helv. Med. Acta 37: 169–174, 1973.
509. HOUSE, P. D. R., POULIS, P., AND WEIDEMANN, M. J.: Isolation of a plasma-membrane subfraction from rat liver containing an insulin-sensitive cyclic-AMP phosphodiesterase. Eur. J. Biochem. 24: 429–437, 1972.
510. HOYUMPA, A. M., PATWARDHAN, R., MAPLES, M., DESMOND, P. V., JOHNSON, R. F., SINCLAIR, A. P., AND SCHENKER, S.: Effect of short-term ethanol administration on lorazepam clearance. Hepatology 1: 47–53, 1981.
511. HSIEH, H. S., AND GANTHER, H. E.: Biosynthesis of dimethyl selenide from sodium selenite in rat liver and kidney cell-free systems. Biochim. Biophys. Acta 497: 205–217, 1977.
512. HUANGE, I.-Y., YOSHIDA, A., TSUNOO, H., AND NAKAJIMA, H.: Mouse liver metallothioneins: Complete amino acid sequence of metallothionein-I. J. Biol. Chem. 252: 8217–8221, 1977.
513. HUBBARD, A. L., AND STUKENBROK, H.: An electron microscope autoradiographic study of the carbohydrate recognition system in the rat liver. II. Intracellular fates of the ^{125}I-ligands. J. Cell Biol. 83: 65–81, 1979.
514. HUCKLE, K. R., CHIPMAN, J. K., HUTSON, H. H., AND MILLBURN, P.: Metabolism of 3-phenoxybenzoic acid and the enterohepatorenal disposition of its metabolites in the rat. Drug Metab. Dispos. 9: 360–368, 1981.
515. HUET, P. M., AND LELORIE, J.: Effects of smoking and chronic hepatitis B on lidocaine and indocyanine green kinetics. Clin. Pharmacol. Ther. 28: 208–215, 1980.
516. HUGHES, R., MILLBURN, P., AND WILLIAMS, R.: Molecular weight as a factor in the excretion of monoquaternary ammonium cations in the bile of the rat, rabbit and guinea pig. Biochem. J. 136: 967–978, 1973.
517. HUMPEL, M., NIEUWEBOER, B., MILIUS, W., HANKE, H., AND WENDT, H.: Kinetics and biotransformation of lormetazepam. II. Radioimmunologic determinations in plasma and urine of young and elderly subjects: First-pass effect. Clin. Pharmacol. Ther. 28: 673–679, 1980.
518. HUNTER, A. L., AND KLAASSEN, C. D.: Species difference in the plasma disappearance and biliary excretion of procaine amide ethobromide. Proc. Soc. Exp. Biol. Med. 139: 1445–1450, 1972.
519. HUNTER, A. L., AND KLAASSEN, C. D.: Biliary excretion of colchicine. J. Pharmacol. Exp. Ther. 192: 605–617, 1975.
520. HUNTER, A. L., AND KLAASSEN, C. D.: Biliary excretion of colchicine in newborn rats. Drug Metab. Dispos. 3: 530–535, 1975.
521. HUNTON, D. B., BOLLMANN, J. L., AND HOFFMANN, H. N.: Studies of hepatic function with indocyanine green. Gastroenterology 39: 713–724, 1960.
522. HWANG, S.: Plasma and hepatic binding of indocyanine green in guinea pigs of different ages. Am. J. Physiol. 228: 7178–724, 1975.
523. HWANG, S. W., AND DIXON, R. L.: Perinatal development of indocyanine green biliary excretion in guinea pigs. Am. J. Physiol. 225: 1454–1459, 1973.
524. HWANG, S. W., AND SCHANKER, L. S.: Hepatic uptake and biliary excretion of N-acetyl procain amide ethobromide in the rat. Am. J. Physiol. 225: 1437–1443, 1973.
525. IGA, T., EATON, D. L., AND KLAASSEN, C. D.: Uptake of unconjugated bilirubin by isolated rat hepatocytes. Am. J. Physiol. 236: C9–C14, 1979.
526. IGA, T., AND KLAASSEN, C. D.: Hepatic extraction of non-metabolizable xenobiotics in rats. J. Pharmacol. Exp. Ther. 211: 690–697, 1979.
527. IGA, T., AND KLAASSEN, C. D.: Age-related pharmacokinetics of ouabain in rats. Proc. Soc. Exp. Biol. Med. 170: 59–62, 1982.
528. IGA, T., AND KLAASSEN, C. D.: Hepatic extraction of bile acids in rats. Biochem. Pharmacol. 31: 205–209, 1982.
529. IGA, T., AND KLAASSEN, C. D.: Uptake of bile acids by isolated rat hepatocytes. Biochem. Pharmacol. 31: 211–216, 1982.
530. IGA, T., YOKOTA, M., SUGIYAMA, Y., AWAZU, S., AND HANANO, M.: Hepatic transport of indocyanine green in rats chronically intoxicated with carbon tetrachloride. Biochem. Pharmacol. 29: 1291–1297, 1980.
531. IKEDA, M., AND UESUGI, T.: Studies on the biliary excretion mechanism of drugs I. Biochem. Pharmacol. 22: 2743–2751, 1973.
532. ILLING, H. P. A.: Critical review: Techniques for microfloral and associated metabolic studies in relation to the absorption and enterohepatic circulation of drugs. Xenobiotica 11: 815–830, 1981.
533. IMAI, K., AND HAYASHI, Y.: Steroid-induced intrahepatic cholestasis in mice. Jpn. J. Pharmacol. 20: 473–481, 1970.
534. IMAMURA, T., AND FUJIMOTO, J. M.: A new mode of action of SKF 525-A on morphine disposition studied by segmented retrograde intrabiliary injection (SRII) in the isolated in situ perfused liver. J. Pharmacol. Exp. Ther. 215: 122–126, 1980.
535. INDACOCHEA-REDMOND, N., AND PLAA, G. L.: Functional effects of α-naphthylisothiocyanate in various species. Toxicol. Appl. Pharmacol. 19: 71–80, 1971.
536. INDACOCHEA-REDMOND, N., WITSCHI, H., AND PLAA, G. L.: Effect of inhibitors of protein and ribonucleic acid synthesis on the hyperbilirubinemia and cholestasis produced by α-naphthylisothiocyanate. J. Pharmacol. Exp. Ther. 184: 780–786, 1973.
537. INDACOCHEA-REDMOND, N., WITSCHI, H., AND PLAA, G. L.: Effects of inhibitors of protein and ribonucleic acid synthesis on α-naphthylisothiocyanate-induced hyperbilirubinemia sulfobromophthalein retention and prolongation of pentobarbital hypnosis. J. Pharmacol. Exp. Ther. 189: 278–284, 1974.
538. INOUE, M., KINNE, R., TRAN, T., AND ARIAS, I. M.: Taurocholate transport by rat liver sinusoidal membrane vesicles: Evidence of sodium cotransport. Hepatology 2: 572–579, 1982.
539. IRELAND, S. J., AND LIVINGSTON, A.: Effect of biliary excretion on ketamine anaesthesia in the rat. Br. J. Anaesth. 52: 23–28, 1980.
540. ISER, J. H., DOWLING, R. H., MOK, H. Y. I., AND BEL, G. D.: Chenodeoxycholic acid treatment of gallstones. N. Engl. J. Med. 293: 378–383, 1975.

541. IWAMOTO, K., EATON, D. L., AND KLAASSEN, C. D.: Uptake of morphine and nalorphine by isolated rat hepatocytes. J. Pharmacol. Exp. Ther. **206:** 181–189, 1978.
542. IWAMOTO, K., AND KLAASSEN, C. D.: First-pass effect of morphine in rats. J. Pharmacol. Exp. Ther. **200:** 236–244, 1977.
543. IWAMOTO, K., AND KLAASSEN, C. D.: First-pass effect of nalorphine in rats. J. Pharmacol. Exp. Ther. **203:** 365–376, 1977.
544. IWAMURA, K.: Clinical studies on cheno- and ursodeoxycholic acid treatment for gallstone dissolution. Hepato-gastroenterology **27:** 26–34, 1980.
545. JACKMAN, G. P., MCLEAN, A. J., JENNINGS, G. L., AND BOBIK, A.: No stereoselective first-pass hepatic extraction of propranolol. Clin. Pharmacol. Ther. **30:** 291–296, 1981.
546. JACKSON, D. V., CASTLE, M. C., AND BENDER, R. A.: Biliary excretion of vincristine. Clin. Pharmacol. Ther. **24:** 101–107, 1978.
547. JACKSON, G. D. F., LEMAITRE-COELHO, I., VAERMAN, J.-P., BAZIN, H., AND BECKERS, A.: Rapid disappearance from serum of intravenously injected rat myeloma IgA and its secretion into bile. Eur. J. Immunol. **8:** 123–126, 1978.
548. JACOBS, S., HAZUM, E., AND CUATRECASAS, P.: The subunit structure of rat liver insulin receptor. Antibodies directed against the insulin-binding subunit. J. Biol. Chem. **255:** 6937–6940, 1980.
549. JAKOBY, W. B., AND HABIG, W. H.: Glutathione transferases. *In* Enzymatic Basis of Detoxication, vol. II, ed. by W. B. Jakoby, pp. 63–94, Academic Press, New York, 1980.
550. JAMES, O., CULLEN, J., BOUCHIER, I. A. D.: Chenodeoxycholic acid therapy for gallstones: Effectiveness, toxicity and influence on bile acid metabolism. Q. J. Med. **44:** 349–367, 1975.
551. JAMES, R., DESMOND, P., KUPFER, A., SCHENKER, S., AND BRANCH, R. A.: The differential localization of various drug metabolizing systems within the rat liver lobule as determined by the hepatotoxins allyl alcohol, carbon tetrachloride and bromobenzene. J. Pharmacol. Exp. Ther. **217:** 127–132, 1981.
552. JANSEN, M., OLSON, J. R., FUJIMOTO, J. M.: Taurolithocholate-induced increase in the intrabiliary pressure generated during retrograde intrabiliary infusion of saline in rats: Antagonism by taurocholate and glycocholate. Toxicol. Appl. Pharmacol. **54:** 9–19, 1980.
553. JAVITT, N. B.: Phenol-3,6-dibromphthalein disulfonate, a new compound for the study of liver disease. Proc. Soc. Exp. Biol. Med. **117:** 254–257, 1964.
554. JAVITT, N. B.: Cholestasis in rats induced by taurolithocholate. Nature (Lond.) **210:** 1262–1263, 1966.
555. JAVITT, N. B.: Current status of cholestasis induced by monohydroxy bile acid. *In* Jaundice, ed. by C. A. Goresky and M. M. Fisher, pp. 401–409, Plenum Press, New York, 1975.
556. JAVITT, N. B.: Hepatic bile formation. N. Engl. J. Med. **295:** 1464–1469, 1511–1516, 1976.
557. JAVITT, N. B., AND EMERMAN, S.: Effect of sodium taurolithocholate on bile flow and bile acid excretion. J. Clin. Invest. **47:** 1002–1014, 1968.
558. JEAN, F., FOLIOT, A., CELIER, C., HOUSSET, E., AND ETIENNE, J.-P.: Influence of clofibrate on hepatic transport of bilirubin and bromosulfophthalein in rats. Biochem. Biophys. Res. Commun. **86:** 1154–1160, 1979.
559. JIRSA, M., AND RABAN, P.: Metabolism of rose bengal. Nature (Lond.) **195:** 1100–1101, 1962.
560. JOHANNESSEN, W., GADEHOLT, G., AND AARBAKKE, J.: Effects of diethyl ether anaesthesia on the pharmacokinetics of antipyrine and paracetamol in the rat. J. Pharm. Pharmacol. **33:** 365–368, 1981.
561. JOHNS, W. H., AND BATES, T. R.: Quantification of the binding tendencies of cholestyramine. I. Effect of structure and added electrolytes on the binding of conjugated and unconjugated bile-salt anions. J. Pharm. Sci. **58:** 179–183, 1969.
562. JONES, A. L., HULING, S., HRADEK, G. T., GAINES, H. S., CHRISTIANSEN, W. D., AND UNDERDOWN, B. J.: Uptake and intracellular disposition of IgA by rat hepatocytes in monolayer culture. Hepatology **2:** 769–776, 1982.
563. JONES, A. L., HRADEK, G. T., RENSTON, R. H., WONG, K. Y., KARLAGANIS, G., AND PAUMGARTNER, G.: Autoradiographic evidence for hepatic lobular concentration gradient of bile acid derivative. Am. J. Physiol. **238:** G233–G237, 1980.
564. JONES, A. L., RENSTON, R. H., SCHMUCKER, D. L., MOONEY, J. S., OCKNER, R. K., AND ADLER, D.: A morphologic evaluation of the pericanalicular cytoplasm in the rat hepatocyte: Demonstrating possible components of the bile secretory apparatus. *In* The Liver. Quantitative Aspects of Structure and Function, ed. by R. Preisig and J. Bircher, pp. 63–70, Edito Cantor, Aulendorf, 1978.
565. JONES, A. L., SCHMUCKER, D. L., MOONEY, J. S., ADLER, R. D., AND OCKNER, R. K.: Morphometric analysis of rat hepatocytes after total biliary obstruction. Gastroenterology **71:** 1050–1060, 1976.
566. JONES, A. L., SCHMUCKER, D. L., RENSTON, R. H., AND MURAKAMI, T.: The architecture of bile secretion: A morphological perspective of physiology. Digest. Dis. Sci. **25:** 609–629, 1980.
567. JONES, R. S., GEIST, R. E., AND HALL, A. D.: The choleretic effects of glucagon and secretin in the dog. Gastroenterology **60:** 64–68, 1971.
568. JONES, R. S., AND GROSSMAN, M. I.: The choleretic response to feeding in dogs. Proc. Soc. Exp. Biol. Med. **132:** 708–711, 1969.
569. JONES, R. S., AND GROSSMAN, M. I.: Choleretic effects of cholecystokinin, gastrin II, and caerulein in the dog. Am. J. Physiol. **219:** 1014–1018, 1970.
570. JONES, R. S., AND MEYERS, W. C.: Regulation of hepatic biliary secretion. Annu. Rev. Physiol. **41:** 67–82, 1979.
571. JOSEPH, S. K., BRADFORD, N. M., AND MCGIVAN, J. D.: Characteristics of the transport of alanine, serine and glutamine across the plasma membrane of isolated rat liver cells. Biochem. J. **176:** 827–836, 1978.
572. JUNGERMANN, K., AND SASSE, D.: Heterogeneity of liver parenchymal cells. Trends Biochem. Sci. **3:** 198–202, 1978.
573. KAGI, J. H. R., HIMMELHOCH, S., WHANGER, P., BETHUNE, J., AND VALLEE, B.: Equine hepatic and renal metallothioneins: Purification, molecular weight, amino acid composition and metal content. J. Biol. Chem. **249:** 3537–3542, 1974.
574. KAGI, J., AND VALLEE, B.: Metallothionein: A cadmium- and zinc-containing protein from equine renal cortex. II. Physicochemical properties. J. Biol. Chem. **236:** 2435–2442, 1961.
575. KAKIS, G., PHILLIPS, M. J., AND YOUSEF, I. M.: The respective roles of membrane cholesterol and of sodium-potassium adenosine triphosphatase in the pathogenesis of lithocholate-induced cholestasis. Lab. Invest. **43:** 73–81, 1980.
576. KAKIS, G., AND YOUSEF, I. M.: Pathogenesis of lithocholate- and taurolithocholate-induced intrahepatic cholestasis in rats. Gastroenterology **75:** 595–607, 1978.
577. KAKIS, G., AND YOUSEF, I. M.: Mechanism of cholic acid protection in lithocholate-induced intrahepatic cholestasis in rats. Gastroenterology **78:** 1402–1411, 1980.
578. KAMINSKI, D. L., AND DESHPANDE, Y. G.: Effect of gastrin I and gastrin II on canine bile flow. Am. J. Physiol. **236:** E584–E588, 1979.
579. KAMINSKI, D. L., DORIGHI, J., AND JELLINEK, M.: Effect of electrical vagal stimulation on canine hepatic bile flow. Am. J. Physiol. **227:** 487–493, 1974.
580. KAMINSKI, D. L., ROSE, R. C., AND NAHRWOLD, D. L.: Effect of pentagastrin on canine bile flow. Gastroenterology **64:** 630–633, 1973.
581. KAMINSKI, D. L., RUWART, M. J., AND JELLINEK, M.: Effect of glucagon on secretin-stimulated bile flow. Am. J. Physiol. **229:** 1480–1485, 1975.
582. KAMINSKI, D. L., RUWART, M. J., AND JELLINEK, M.: Effect of the histamine (H_2) inhibitor metiamide on histamine stimulated bile flow in dogs. Am. J. Physiol. **231:** 516–521, 1976.
583. KAMISAKA, K., LISTOWSKY, I., AND ARIAS, I. M.: Circular dichroism studies of Y protein (ligandin), a major organic anion binding protein in liver, kidney and small intestine. Ann. N.Y. Acad. Sci. **226:** 148–153, 1973.
584. KAMISAKA, K., LISTOWSKY, I., GATMAITAN, Z., AND ARIAS, I. M.: Interactions of bilirubin and other ligands with ligandin. Biochemistry **14:** 2175–2180, 1975.
585. KAMISAKA, K., LISTOWSKY, I., GATMAITAN, Z., AND ARIAS, I. M.: Circular dichroism analysis of the secondary structure of Z protein and its complexes with bilirubin and other organic anions. Biochim. Biophys. Acta **393:** 24–30, 1975.
586. KAPLOWITZ, N.: Physiological significance of glutathione S-transferases. Am. J. Physiol. **239:** 439–444, 1980.
587. KAPLOWITZ, N.: The importance and regulation of hepatic glutathione. Yale J. Biol. Med. **54:** 497–502, 1981.
588. KAPLOWITZ, N., EBERLE, D. E., PETRINI, J., TOULOUKIAN, J., CORVASCE, M. C., AND KUHLENKAMP, J.: Factors influencing the efflux of hepatic glutathione into bile in rats. J. Pharmacol. Exp. Ther. **224:** 141–147, 1983.
589. KAPLOWITZ, N., PERCY-ROBB, I. W., AND JAVITT, N. B.: Role of hepatic anion-binding protein in bromsulphthalein conjugation. J. Exp. Med. **138:** 483–487, 1973.
590. KASPER, C. B., AND HENTON, D.: Glucuronidation. *In* Enzymatic Basis of Detoxication, ed. by W. B. Jakoby, vol. II, pp. 4–36, Academic Press, New York, 1980.
591. KATO, A.: Sex-related differences in drug metabolism. Drug Metab. Rev. **3:** 1–32, 1974.
592. KATZUNG, B. G., AND MEYERS, F. H.: Excretion of radioactive digitoxin by the dog. J. Pharmacol. Exp. Ther. **149:** 257–262, 1965.
593. KATZUNG, B. G., AND MEYERS, F. H.: Biotransformation of digitoxin in the dog. J. Pharmacol. Exp. Ther. **154:** 575–580, 1966.
594. KAYE, C. M.: The biliary excretion of acebutolol in man. J. Pharm. Pharmacol. **28:** 449–450, 1976.
595. KEEFFEE, E. B., SCHARSCHMIDT, B. F., BLANKENSHIP, N. M., AND OCKNER, R. K.: Studies of relationships among bile flow, liver plasma membrane NaK-ATPase, and membrane microviscosity in the rat. J. Clin. Invest. **64:** 1590–1598, 1979.
596. KEHOE, R. A.: The metabolism of lead in man in health and disease. Arch. Environ. Health **2:** 418–422, 1961.
597. KEIDING, S., AND ANDREASEN, P. B.: Hepatic clearance measurements and pharmacokinetics. Pharmacology **19:** 105–110, 1979.
598. KENDLER, J., ANURAS, S., LABORDA, O., AND ZIMMERMAN, H. J.: Perfusion of the isolated rat liver with erythromycin estolate and other derivatives. Proc. Soc. Exp. Biol. Med. **139:** 1272–1275, 1972.
599. KENDLER, J., BOWRY, S., SEEFF, L. B., AND ZIMMERMAN, H. J.: Effect of

chlorpromazine on the function of the perfused isolated liver. Biochem. Pharmacol. **20:** 2439–2445, 1971.
600. KENWRIGHT, S., AND LEVI, A. J.: Sites of competition in the selective hepatic uptake of rifamycin-SV, flavaspidic acid, bilirubin and bromsulphthalein. Gut **15:** 220–226, 1974.
601. KETLEY, J. N., HABIG, W. H., AND JAKOBY, W. B.: Binding of nonsubstrate ligands to the glutathione S-transferases. J. Biol. Chem. **250:** 8670–8673, 1975.
602. KEY, P. H., BONORRIS, G. G., MARKS, J. W., CHUNG, A., AND SCHOENFIELD, L. J.: Biliary lipid synthesis and secretion in gallstone patients before and during treatment with chenodeoxycholic acid. J. Lab. Clin. Med. **95:** 816–826, 1980.
603. KHANDUJA, K. L., DOGRA, S. C., AND SHARMA, R. R.: Glucuronic acid conjugates of metabolites of 7,12-dimethylbenz(a)anthracene excreted through bile ducts in rat. Indian J. Exp. Biol. **19:** 375–378, 1981.
604. KILLENBERG, P. G., AND HOPPEL, C. L.: Inhibition of rat liver mitochondrial oxidative phosphorylation by sulfobromophthalein. Mol. Pharmacol. **10:** 108–118, 1974.
605. KIMURA, M., OTAKI, N., YOSHIKI, S., SUZUKI, M., HORIUCHI, N., AND SUDA, T.: The isolation of metallothionein and its protective role in cadmium poisoning. Arch. Biochem. Biophys. **165:** 340–348, 1974.
606. KINGSLEY, B. S., AND FRAZIER, J. M.: Cadmium transport in isolated perfused rat liver: Zinc-cadmium competition. Am. J. Physiol. **236:** C139–C143, 1979.
607. KINO, K., TSUNOO, H., HIGA, Y., TAKAMI, M., HAMAGUCHI, H., NAKAJIMA, H.: Hemoglobin-haptoglobin receptor in rat liver plasma membrane. J. Biol. Chem. **255:** 9616–9620, 1980.
608. KIRSHENBAUM, G., SHAMES, D. M., AND SCHMID, R.: An expanded model of bilirubin kinetics: Effect of feeding, fasting and phenobarbital in Gilbert's syndrome. J. Pharmacokinet. Biopharm. **4:** 115–155, 1976.
609. KITANI, K.: Functional aspects of the aging liver. *In* Liver and Aging, ed. by D. Platt, and F. K. Schattauer, pp. 5–17, Verlag, New York, 1977.
610. KITANI, K.: Liver and Aging—1978, Elsevier, New York, 1978.
611. KITANI, K., AND KANAI, S.: Biliary transport maximum of tauroursodeoxycholate is twice as high as that of taurocholate in the rat. Life Sci. **29:** 269–275, 1981.
612. KITANI, K., AND KANAI, S.: Tauroursodeoxycholate prevents taurocholate induced cholestasis. Life Sci. **30:** 515–523, 1982.
613. KITANI, K., KANAI, S., AND MIURA, R.: Increased biliary excretion of ouabain induced by bucolome in the rat. Clin. Exp. Pharmacol. Physiol. **5:** 117–124, 1978.
614. KITANI, K., KANAI, S., MIURA, R., MORITA, Y., AND KASAHARA, M.: The effect of aging on the biliary excretion of ouabain in the rat. Exp. Gerontol. **13:** 9–17, 1978.
615. KITANI, K., MIURA, R., AND KANAI, S.: Difference in the effect of bucolome on the hepatic transport maximum of sulfobromophthalein and indocyanine green. Tohoku J. Exp. Med. **126:** 247–256, 1978.
616. KITANI, K., MORITA, Y., AND KANAI, S.: The effects of spironolactone on the biliary excretion of mercury, cadmium, zinc, and cerium in rats. Biochem. Pharmacol. **26:** 279–282, 1977.
617. KITANI, K., MORITA, Y., MIURA, R., AND KANAI, S.: Bile-salt-dependent and independent choleresis induced by bucolome in the rat. Can. J. Physiol. Pharmacol. **55:** 1155–1161, 1977.
618. KITANI, K., NOKUBO, M., KANAI, S., MIURA, R., AND UESUGI, T.: The biliary excretion of bucolome in the rat. A possible cause for choleresis. Biochem. Pharmacol. **26:** 2457–2461, 1977.
619. KLAASSEN, C. D.: Biliary flow after microsomal enzyme induction. J. Pharmacol. Exp. Ther. **168:** 218–223, 1969.
620. KLAASSEN, C. D.: Plasma disappearance and biliary excretion of sulfobromophthalein and phenol-3,6-dibromophthalein disulfonate after microsomal enzyme induction. Biochem. Pharmacol. **19:** 1241–1249, 1970.
621. KLAASSEN, C. D.: Effects of phenobarbital on the plasma disappearance and biliary excretion of drugs in rats. J. Pharmacol. Exp. Ther. **175:** 289–300, 1970.
622. KLAASSEN, C. D.: Studies on the increased biliary flow produced by phenobarbital in rats. J. Pharmacol. Exp. Ther. **176:** 743–751, 1971.
623. KLAASSEN, C. D.: Does bile acid secretion determine canalicular bile production in rats? Am. J. Physiol. **220:** 667–673, 1971.
624. KLAASSEN, C. D.: Species difference in the choleretic response to bile salts. J. Physiol. **224:** 259–269, 1972.
625. KLAASSEN, C. D.: Immaturity of the newborn rat's hepatic excretory function for ouabain. J. Pharmacol. Exp. Ther. **183:** 520–526, 1972.
626. KLAASSEN, C. D.: Comparison of the toxicity of chemicals in newborn rats, to bile duct-ligated and sham-operated rats and mice. Toxicol. Appl. Pharmacol. **24:** 37–44, 1973.
627. KLAASSEN, C. D.: The effect of altered hepatic function on the toxicity, plasma disappearance and biliary excretion of diethylstilbestrol. Toxicol. Appl. Pharmacol. **24:** 142–149, 1973.
628. KLAASSEN, C. D.: Effect of alteration in body temperature on the biliary excretion of copper. Proc. Soc. Exp. Biol. Med. **144:** 8–12, 1973.
629. KLAASSEN, C. D.: Hepatic excretory function in the newborn rat. J. Pharmacol. Exp. Ther. **184:** 721–728, 1973.
630. KLAASSEN, C. D.: Comparison of the choleretic properties of bile acids. Eur. J. Pharmacol. **23:** 270–275, 1973.
631. KLAASSEN, C. D.: Immaturity of the hepatic excretory function for ouabain. *In* The Liver. Quantitative Aspects of Structure and Function, ed. by G. Paumgartner and R. Preisig, pp. 402–410, S. Karger, Basel, 1973.
632. KLAASSEN, C. D.: Bile flow and composition during bile acid depletion and administration. Can. J. Physiol. Pharmacol. **52:** 334–348, 1974.
633. KLAASSEN, C. D.: Biliary excretion of arsenic in rats, rabbits, and dogs. Toxicol. Appl. Pharmacol. **29:** 447–457, 1974.
634. KLAASSEN, C. D.: Biliary excretion of manganese in rats, rabbits, and dogs. Toxicol. Appl. Pharmacol. **29:** 458–468, 1974.
635. KLAASSEN, C. D.: Comparison of the effects of two-thirds hepatectomy and bile-duct ligation on hepatic excretory function. J. Pharmacol. Exp. Ther. **191:** 25–31, 1974.
636. KLAASSEN, C. D.: Effect of microsomal enzyme inducers on the biliary excretion of cardiac glycosides. J. Pharmacol. Exp. Ther. **191:** 201–211, 1974.
637. KLAASSEN, C. D.: Stimulation of the development of the hepatic excretory mechanism for ouabain in newborn rats with microsomal enzyme inducers. J. Pharmacol. Exp. Ther. **191:** 212–218, 1974.
638. KLAASSEN, C. D.: Biliary excretion of drugs: Role of ligandin in newborn immaturity and in the action of microsomal enzyme inducers. J. Pharmacol. Exp. Ther. **195:** 311–319, 1975.
639. KLAASSEN, C. D.: Biliary excretion of mercury compounds. Toxicol. Appl. Pharmacol. **33:** 356–365, 1975.
640. KLAASSEN, C. D.: Biliary excretion of xenobiotics. *In* Critical Reviews in Toxicology, ed. by L. Goldberg, vol. 4, pp. 1–29, CRC Press, Inc., Cleveland, OH, 1975.
641. KLAASSEN, C. D.: Effect of spironolactone on the distribution of mercury. Toxicol. Appl. Pharmacol. **33:** 366–375, 1975.
642. KLAASSEN, C. D.: Extrahepatic distribution of sulfobromophthalein. Can. J. Physiol. Pharmacol. **53:** 120–123, 1975.
643. KLAASSEN, C. D.: Hepatic uptake of cardiac glycosides in newborn rats, rabbits and dogs. Biochem. Pharmacol. **24:** 923–925, 1975.
644. KLAASSEN, C. D.: Biliary excretion of metals. Drug Metab. Rev. **5:** 165–196, 1976.
645. KLAASSEN, C. D.: Effect of microsomal enzyme inducers on the biliary excretion of an exogenous load of bilirubin in newborn rats. Proc. Soc. Exp. Biol. Med. **153:** 370–373, 1976.
646. KLAASSEN, C. D.: Pharmacokinetics of rose bengal in the rat, rabbit, dog and guinea pig. Toxicol. Appl. Pharmacol. **38:** 85–100, 1976.
647. KLAASSEN, C. D.: Studies on the mechanism of spironolactone protection against indomethacin toxicity. Toxicol. Appl. Pharmacol. **38:** 127–135, 1976.
648. KLAASSEN, C. D.: Biliary excretion. *In* Handbook of Physiology, Section 9: Reactions to Environmental Agents, ed. by D. H. K. Lee, pp. 537–553, American Physiological Society, Washington, DC, 1977.
649. KLAASSEN, C. D.: Effect of metallothionein on the hepatic disposition of metals. Am. J. Physiol. **234:** E47–E53, 1978.
650. KLAASSEN, C. D.: Development of hepatic excretory function in the newborn rat. *In* Liver and Aging, ed. by K. Kitani, pp. 313–323, Elsevier, Amsterdam, 1978.
651. KLAASSEN, C. D.: Independence of bile acid and ouabain hepatic uptake: studies in the newborn rat. Proc. Soc. Exp. Biol. Med. **157:** 66–69, 1978.
652. KLAASSEN, C. D.: Biliary excretion of silver in the rat, rabbit and dog. Toxicol. Appl. Pharmacol. **50:** 49–55, 1979.
653. KLAASSEN, C. D.: Importance of hepatic function on the plasma disappearance and biliary excretion of hexachlorophene. Toxicol. Appl. Pharmacol. **49:** 113–117, 1979.
654. KLAASSEN, C. D.: Effect of spironolactone on the biliary excretion and distribution of metals. Toxicol. Appl. Pharmacol. **50:** 41–48, 1979.
655. KLAASSEN, C. D.: Induction of metallothionein by adrenocortical steroids. Toxicology **20:** 275–279, 1981.
656. KLAASSEN, C. D., AND CAGEN, S. Z.: Metallothionein as a trap for reactive organic intermediates. *In* Biological Reactive Intermediates. II, part A, ed. by R. Snyder, D. V. Parke, J. J. Kocsis, D. J. Jollow, C. G. Gibson, and C. Witmar, pp. 633–646, Plenum Press, New York, 1982.
657. KLAASSEN, C. D., EATON, D. L., AND CAGEN, S. Z.: Hepatobiliary disposition of xenobitics. *In* Progress in Drug Metabolism, ed. by J. W. Bridges and L. F. Chasseaud, pp. 1–75, John Wiley and Sons, New York, 1981.
658. KLAASSEN, C. D., AND FITZGERALD, T. J.: Metabolism and biliary excretion of ethacrynic acid. J. Pharmacol. Exp. Ther. **191:** 548–556, 1974.
659. KLAASSEN, C. D., AND KOTSONIS, F. N.: Biliary excretion of cadmium in the rat, rabbit, and dog. Toxicol. Appl. Pharmacol. **41:** 101–112, 1977.
660. KLAASSEN, C. D., AND PLAA, G. L.: Species variation in metabolism, storage and excretion of sulfobromophthalein. Am. J. Physiol. **213:** 1322–1326, 1967.
661. KLAASSEN, C. D., AND PLAA, G. L.: Effect of carbon tetrachloride on the metabolism, storage, and excretion of sulfobromophthalein. Toxicol. Appl. Pharmacol. **12:** 132–139, 1968.
662. KLAASSEN, C. D., AND PLAA, G. L.: Hepatic disposition of phenoldibromophthalein disulfonate and sulfobromophthalein. Am. J. Physiol. **215:** 971–976, 1968.
663. KLAASSEN, C. D., AND PLAA, G. L.: Studies on the mechanism of phenobarbital-enhanced sulfobromophthalein disappearance. J. Pharmacol. Exp. Ther. **161:** 361–366, 1968.
664. KLAASSEN, C. D., AND PLAA, G. L.: Plasma disappearance and biliary

excretion of indocyanine green in rats, rabbits and dogs. Toxicol. Appl. Pharmacol. **15:** 374–384, 1969.
665. KLAASSEN, C. D., AND SHOEMAN, D. W.: Biliary excretion of lead in rats, rabbits and dogs. Toxicol. Appl. Pharmacol. **29:** 434–446, 1974.
666. KLAASSEN, C. D., AND STACEY, N. H.: Use of isolated hepatocytes in toxicity assessment. *In* Toxicology of the Liver, ed. by G. L. Plaa and W. R. Hewitt, pp. 147–179, Raven Press, New York, 1982.
667. KLAASSEN, C. D., AND STROM, S. C.: Comparison of biliary excretory function and bile composition in male, female, and lactating female rats. Drug Metab. Dispos. **6:** 120–124, 1978.
668. KLAASSEN, C. D., AND WONG, K.-L.: Minimal role of the high concentration of hepatic metallothionein in the newborn rat in the toxicity, distribution, and excretion of cadmium. *In* Biological Roles of Metallothionein, ed. by E. Foulkes, pp. 113–130, Elsevier-North Holland, New York, 1982.
669. KLATSKIN, G.: Drug induced hepatic injury. *In* The Liver and Its Diseases, ed. by F. Schaffner, S. Sherlock and C. M. Leevy, pp. 163–178, Intercontinental Medical Book Corp., New York, 1974.
670. KLEEBERG, U., FISCHER, E., GREGUS, Z., KLINGER, W., AND VARGA, F.: Effect of 3-methylcholanthrene on the biliary excretion of bromosulphthalein and eosine in newborn rats. Acta Physiol. Acad. Sci. Hung. **53:** 363–367, 1979.
671. KLEINMAN, R. E., HARMATZ, P. R., AND WALKER, W. W.: The liver: An integral part of the enteric mucosal immune system. Hepatology **2:** 379–384, 1982.
672. KLOTZ, U., AND ANTONIN, K. H.: Biliary excretion studies with digoxin in man. Int. J. Clin. Pharmacol. Biopharm. **15:** 332–334, 1977.
673. KNODELL, R. G.: Effects of chlorpromazine on bilirubin metabolism and biliary secretion in the rat. Gastroenterology **69:** 965–972, 1975.
674. KNODELL, R. G.: Alterations in bile flow and Na^+-K^+ biliary excretion induced by theophylline and ethacrynic acid. Proc. Soc. Exp. Biol. Med. **157:** 306–311, 1978.
675. KNODELL, R. G., BROOKS, D. A., ALLEN, R. C., AND KYNER, W. T.: Alterations in pentobarbital and meperidine pharmacokinetics induced by bile duct ligation in the rat. J. Pharmacol. Exp. Ther. **215:** 619–625, 1980.
676. KOJIMA, Y., BERGER, C., VALLEE, B. L., AND KAGI, J. H. R.: Amino-acid sequence of equine renal metallothionein-1B. Proc. Natl. Acad. Sci. U.S.A. **73:** 3413–3417, 1976.
677. KOTSONIS, F. N., AND KLAASSEN, C. D.: Increase in hepatic metallothionein in rats treated with alkylating agent. Toxicol. Appl. Pharmacol. **51:** 19–27, 1979.
678. KOTSONIS, F. N., AND KLAASSEN, C. D.: Metallothionein and its interactions with cadmium. *In* Cadmium in the Environment. Part II, ed. by J. O. Nriagu, pp. 595–616, John Wiley and Sons, New York, 1981.
679. KOTTRA, H. L., AND KAPPAS, A.: Estrogen pharmacology. III. Effect of estradiol on plasma disappearance rate of sulfobromophthalein in man. Arch. Intern. Med. **117:** 373–376, 1966.
680. KOWARSKI, S., BLAIR-STANEK, C. S., AND SCHACHTER, D.: Active transport of zinc and identification of zinc-binding protein in rat jejunal mucosa. Am. J. Physiol. **226:** 401–407, 1974.
681. KRAG, E., AND PHILLIPS, S. F.: Active and passive bile acid absorption in man. Perfusion studies of the ileum and jejunum. J. Clin. Invest. **53:** 1686–1694, 1974.
682. KRAMER, W., BUSCHER, H.-P., GEROK, W., AND KURZ, G.: Bile salt binding to serum components. Taurocholate incorporation into high-density lipoproteins revealed by photoaffinity labelling. Eur. J. Biochem. **102:** 1–9, 1979.
683. KREEK, M. J., PETERSON, R. E., SLEISENGER, M. H., AND JEFFRIES, G. H.: Effects of ethinylestradiol-induced cholestasis on bile flow and biliary excretion of estradiol and estradiol glucuronide by the rat. Proc. Soc. Exp. Biol. Med. **131:** 646–650, 1969.
684. KRELL, H., HOKE, H., AND PFAFF, E.: Development of intrahepatic cholestasis by α-naphthylisothiocyanate in rats. Gastroenterology **82:** 507–514, 1982.
685. KRENNING, E. P., DOCTER, R., BERNARD, H. F., VISSER, T. J., AND HENNEMANN, G.: The essential role of albumin in the active transport of thyroid hormones into primary cultured rat hepatocytes. FEBS Lett. **107:** 227–230, 1979.
686. KRENNING, E. P., DOCTER, R., BERNARD, B., VISSER, T., AND HENNEMAN, G.: Characteristics of active transport of thyroid hormone into rat hepatocytes. Biochim. Biophys. Acta **676:** 314–320, 1981.
687. KRISTENSEN, L. O.: Energization of alanine transport in isolated rat hepatocytes. J. Biol. Chem. **255:** 5236–5243, 1980.
688. KROKER, R.: Influence of rifamycin SV on heptic uptake and secretion of bile acids. Naunyn-Schmiedeberg's Arch. Pharmacol. **297:** R8, 1977.
689. KROKER, R., ANWER, M. S., AND HEGNER, D.: The interaction of rifamycin SV with hepatic transport of taurocholic acid in the isolated perfused rat liver. Naunyn-Schmiedeberg's Arch. Pharmacol. **302:** 323–327, 1978.
690. KUBIN, R. H., GRODSKY, G. M., AND CARBONE, J. V.: Investigation of rose bengal conjugation. Proc. Soc. Exp. Biol. Med. **104:** 650–650, 1960.
691. KUENZLE, C. C.: Bilirubin conjugates in bile. *In* The Hepatobiliary System, ed. by W. Taylor, pp. 309–335, Plenum Press, New York, 1976.
692. KUMAR, R., NAGUBANDI, S., AND LONDOWSKI, J. M.: The enterohepatic physiology of 24,25-dihydroxyvitamin D_3. J. Lab. Clin. Med. **96:** 278–284, 1980.
693. KUMAR, R., NAGUBANDI, S., MATTOX, V. R., AND LONDOWSKI, J. M.: Enterohepatic physiology of 1,25-dihydroxyvitamin D_3. J. Clin. Invest. **65:** 277–284, 1980.
694. KUO, S. H., AND JOHNSON, G. E.: The influence of [^{3}H]-taurocholate on the biliary excretion of [^{14}C]-acetylprocaine amide ethobromide. Can. J. Physiol. Pharmacol. **53:** 888–894, 1975.
695. KUPFERBERG, H. J.: Inhibition of ouabain-^{3}H uptake by liver slices and its excretion into the bile by compounds having a steroid nucleus. Life Sci. **8:** 1179–1185, 1969.
696. KUPFERBERG, H. J., AND SCHANKER, L. S.: Biliary secretion of ouabain-^{3}H and its uptake by liver slices in the rat. Am. J. Physiol. **214:** 1048–1053, 1968.
697. KUTZ, K., SCHULTE, A., JUST, C., LINSTAEDT, AND REITER, B.: Bile formation and biliary lipid composition under the influence of clofibrate and phenobarbital pretreatment in the rat. Naunyn-Schmiedeberg's Arch. Pharmacol. **308:** 171–177, 1979.
698. LAATIKAINEN, T.: Excretion of neutral steroid hormones in human bile. Ann. Clin. Res. **2**(suppl. 5): 1–28, 1970.
699. LAATIKAINEN, T., AND KARJALAINEN, O.: Excretion of progesterone metabolites in urine and bile of pregnant women with intrahepatic cholestasis. J. Steroid Biochem. **4:** 641–648, 1973.
700. LAATIKAINEN, T., LEHTONEN, P., AND HESSO, A.: Biliary bile acids in uncomplicated pregnancy and in cholestasis of pregnancy. Clin. Chim. Acta **85:** 145–150, 1978.
701. LACK, L.: Properties and biological significance of the ileal bile salt transport system. Environ. Health Perspect. **33:** 79–90, 1979.
702. LAGARDE, S., ELIAS, E., WADE, J. B., AND BOYER, J. L.: Structural heterogeneity of hepatocyte "tight" junctions: A quantitative analysis. Hepatology **1:** 193–203, 1981.
703. LAPERCHE, Y., GRAILLOT, C., ARONDEL, J., AND BERTHELOT, P.: Uptake of rifampicin by isolated rat liver cells. Interaction with sulfobromophthalein uptake and evidence for separate carriers. Biochem. Pharmacol. **28:** 2065–2069, 1979.
704. LAPERCHE, Y., LAUNAY, A., OUDEA, P., DOULIN, A., AND BARAUD, J.: Effects of phenobarbital and rose bengal on the ATPases of plasma membranes of rat and rabbit liver. Gut **13:** 920–925, 1972.
705. LAPERCHE, Y., AND OUDEA, P.: Inhibition of sulfobromophthalein of mitochondrial translocation of anions and adenine nucleotides: Effects upon liver adenosine triphosphate and possible correlation with inhibition of bile flow in the rat. J. Pharmacol. Exp. Ther. **197:** 235–244, 1976.
706. LAPERCHE, Y., OUDEA, M.-C., AND LOSTANLEN, D.: Toxic effects of indocyanine green on rat liver mitochondria. Toxicol. Appl. Pharmacol. **41:** 377–387, 1977.
707. LAPERCHE, Y., PREAUX, A. M., AND BERTHELOT, P.: Two systems are involved in the sulfobromophthalein uptake by rat liver cells: One is shared with bile salts. Biochem. Pharmacol. **30:** 1333–1336, 1981.
708. LAPERCHE, Y., PREAUX, A. M., FELDMANN, G., MAHU, J. L., AND BERTHELOT, P.: Effect of fasting on organic anion uptake by isolated rat liver cells. Hepatology **1:** 617–621, 1981.
709. LARNER, J., LAWRENCE, J. C., ROACH, P. J., DEPAOLI-ROACH, A. A., WALKENBACH, R. J., GUINOVART, J., AND HAZEN, R. J.: About insulin and glycogen. *In* Cold Spring Harbor Symposium on Cell Proliferation, pp. 95–112, Cold Spring Harbor, New York, 1979.
710. LARUSSO, N. F., AND FOWLER, S.: Coordinate secretion of acid hydrolases in rat bile. Hepatocyte exocytosis of lysosomal protein? J. Clin. Invest. **64:** 948–954, 1979.
711. LARUSSO, N. F., KOST, L. J., CARTER, J. A., AND BARHAM, S. S.: Triton WR-1339, a lysosomatotropic compound, is excreted into bile and alters the biliary excretion of lysosomal enzyme and lipids. Hepatology **2:** 209–215, 1982.
712. LARUSSO, N. F., LINDMARK, D. G., AND MULLER, M.: Biliary and renal excretion, hepatic metabolism, and hepatic subcellular distribution of metronidazole in the rat. Biochem. Pharmacol. **27:** 2247–2254, 1978.
713. LARSEN, G. L., AND BAKKE, J. E.: Enterohepatic circulation in formation of propachlor (2-chloro-N-isopropylacetanilide) metabolites in the rat. Xenobiotica **11:** 473–480, 1981.
714. LARSSON-COHN, U., AND STENRAM, U.: Jaundice during treatment with oral contraceptive agents. J.A.M.A. **193:** 422–426, 1965.
715. LATHAM, P. S., AND KASHGARIAN, M.: The ultrastructural localization of transport ATPase in the rat liver at non-bile canicular plasma membrane. Gastroenterology **76:** 988–996, 1979.
716. LAUTERBURG, B. H., AND MITCHELL, J. R.: Toxic doses of acetaminophen suppress hepatic glutathione synthesis in rats. Hepatology **2:** 8–12, 1982.
717. LAYDEN, T. J., AND BOYER, J. L.: The effect of thyroid hormone on bile salt-independent bile flow and Na^+,K^+-ATPase activity in liver plasma membranes enriched in bile canaliculi. J. Clin. Invest. **57:** 1009–1018, 1976.
718. LAYDEN, T. J., AND BOYER, J. L.: Taurolithocholate-induced cholestasis: Taurocholate, but not dehydrocholate, reverses cholestasis and bile canalicular membrane injury. Gastroenterology **73:** 120–128, 1977.
719. LAYDEN, T. J., AND BOYER, J. L.: Bile acids influence bile canalicular

membrane morphology and the lobular gradient in canalicular size. Lab. Invest. **39:** 110–119, 1978.
720. LAYDEN, T. J., ELIAS, E., AND BOYER, J. L.: Bile formation in the rat. The role of the paracellular shunt pathway. J. Clin. Invest. **62:** 1375–1385, 1978.
721. LECAM, A., AND FREYCHET, P.: Neutral amino acid transport. Characterization of the A and L systems in isolated rat hepatocytes. J. Biol. Chem. **252:** 148–156, 1977.
722. LECAM, A., REY, J. F., FEHLMANN, M., KITBGI, P., AND FREYCHET, P.: Amino acid transport in isolated hepatocytes after partial hepatectomy in the rat. Am. J. Physiol. **236:** E594–E602, 1979.
723. LEES, A. W., ASGHER, B., HASHEM, M. A., AND SINHA, B. N.: Jaundice after rifampicin. Br. J. Dis. Chest. **64:** 90–95, 1970.
724. LEEVY, C. M., BENDER, J., SILVERBERG, M., AND NAYLOR, J.: Physiology of dye extraction by the liver: Comparative studies of sulfobromophthalein and indocyanine green. Ann. N.Y. Acad. Sci. **111:** 161–175, 1963.
725. LEMAITRE-COELHO, I., JACKSON, G. D. F., AND VAERMAN, J. P.: Rat bile as a convenient source of secretory IgA and free secretory component. Eur. J. Immunol. **7:** 588–590, 1977.
726. LENNON, H. D.: Effect of several anabolic steroids on sulfobromophthalein (BSP) retention in rabbits. Steroids **5:** 361–373, 1965.
727. LENTZ, P. E., AND DILUZIO, N. R.: Biochemical characterization of Kupffer and parenchymal cells isolated from rat liver. Exp. Cell. Res. **67:** 17–26, 1971.
728. LEVI, A. J., GATMAITAN, Z., AND ARIAS, I. M.: Two hepatic cytoplasmic protein fractions, Y and Z, and their possible role in the hepatic uptake of bilirubin, sulfobromophthalein, and other anions. J. Clin. Invest. **48:** 2156–2167, 1969.
729. LEVI, A. J., GATMAITAN, Z., AND ARIAS, I. M.: Deficiency of hepatic organic anion-binding protein, impaired organic anion uptake by liver and "physiologic" jaundice in newborn monkeys. N. Engl. J. Med. **283:** 1136–1139, 1970.
730. LEVINE, R. I., AND HALL, R. C.: Cyclic AMP in secretin choleresis evidence for a regulatory role in man and baboons but not in dogs. Gastroenterology **70:** 537–544, 1976.
731. LEVINE, R. I., REYES, H., LEVI, A. J., GATMAITAN, Z., AND ARIAS, I. M.: Phylogenetic study of organic anion transfer from plasma into liver. Nature (New Biol.) **231:** 277–279, 1971.
732. LEVINE, W. G.: Effect of the hypolipidemic drug nafenopin [2-methyl-2-[*p*-(1,2,3,4,-tetrahydro-1-naphthyl)phenoxyl propionic acid; TPIA; SU-13,437], on the hepatic disposition of foreign compounds in the rat. Drug Metab. Dispos. **2:** 178–185, 1974.
733. LEVINE, W. G.: Biliary excretion of drugs and other xenobiotics. Annu. Rev. Pharmacol. Toxicol. **18:** 81–96, 1978.
734. LEVINE, W. G.: Induction and inhibition of the metabolism and biliary excretion of the azo dye carcinogen, N,N-dimethyl-4-aminoazobenzene (DAB), in the rat. Drug Metab. Dispos. **8:** 212–217, 1980.
735. LEVINE, W. G., AND FINKELSTEIN, T. T.: Biliary excretion of N,N-dimethyl-4-aminoazobenzene (DAB) in the rat. Drug Metab. Dispos. **6:** 265–272, 1978.
736. LEVY, J. C., BESSIN, P., AND LABAUNE, J. P.: Tienilic acid and biliary secretion. Ann. Pharm. Fr. **39:** 27–35, 1981.
737. LEWIS, M. H., BAKER, A. L., DHORAJIWALA, J., AND MOOSSA, A. R.: Secretin enhances [^{14}C]erythritol clearance in unanesthetized dogs. Digest. Dis. Sci. **27:** 57–64, 1982.
738. LEYHAUSEN, G., AND MULLER, W. E.: Liver cytosol protein binding may be not responsible for hepatic uptake of biliary contrast agents. Arch. Int. Pharmacodyn. Ther. **252:** 4–16, 1981.
739. LICHTER, M., FLEISCHNER, G., KIRSCH, R., LEVI, A. J., KAMINSAKA, K., AND ARIAS, I. M.: Ligandin and Z protein in binding of thyroid hormones by the liver. Am. J. Physiol. **230:** 1113–1120, 1976.
740. LIERSCH, M., CZYGAN, P., AND STIEHL, A.: Studies on hepatic uptake and secretion of bile salt sulfates by the isolated perfused rat liver. Digestion **12:** 326–327, 1975.
741. LIN, S. K., MOSS, A. A., AND RIEGELMAN, S.: Iodipamide kinetics: Capacity-limited biliary excretion with simultaneous pseudo-first-order renal excretion. J. Pharm. Sci. **66:** 1670–1674, 1977.
742. LINDBLAD, L., LUNDHOLM, K., AND SCHERSTEN, T.: Bile acid concentrations in systemic and portal serum in presumably normal man and in cholestatic and cirrhotic conditions. Scand. J. Gastroenterol. **12:** 395–400, 1977.
743. LINDBLAD, L., AND SCHERSTEN, T.: Influence of cholic and chenodeoxycholic acid on canalicular bile flow in man. Gastroenterology **70:** 1121–1124, 1976.
744. LINDSTEDT, S.: The turnover of cholic acid in man. Bile acids and steroids 51. Acta Physiol. Scand. **40:** 1–9, 1957.
745. LITWILLER, R. D., MATTOX, V. R., JARDINE, I., AND KUMAR, R.: Evidence for a monoglucuronide of 1,25-dihydroxyvitamin D_3 in rat bile. J. Biol. Chem. **257:** 7491–7494, 1982.
746. LOCK, S., WITSCHI, H. P., AND PLAA, G. L.: Bile production and flow in rats treated with α-naphthylisothiocyanate (ANIT). Can. Fed. Biol. Soc. **19:** 102, 1976.
747. LOCK, S., WITSCHI, H., AND PLAA, G. L.: The effect of cycloheximide on bile flow in rats. Proc. Soc. Exp. Biol. Med. **161:** 546–553, 1979.
748. LOCK, S., WITSCHI, H., SKELTON, F. S., HANASONO, G., AND PLAA, G. L.: Effect of cycloheximide on the distribution of α-naphthylisothiocyanate in rats. Exp. Mol. Pharmacol. **21:** 237–245, 1974.
749. LOEB, P. M., BARNHART, J. L., AND BERK, R. N.: Dependence of the biliary excretion of iopanoic acid on bile salts. Gastroenterology **74:** 174–181, 1978.
750. LOEB, P. M., BERK, R. N., COBO-FRENKEL, A., AND BARNHART, J. L.: The biliary and urinary excretion and the choleretic effect of ioglycamide in dogs. Invest. Radiol. **11:** 449–458, 1976.
751. LOFFLER, S., AND BOLT, H. M.: Studies on enterohepatic circulation of estradiol and ethinylestradiol in the rat. Arzneim.-Forsch. **30:** 810–813, 1980.
752. LONDON, C. D., DIAMOND, J. M., AND BROOKS, F. P.: Electrical potential difference in the biliary tree. Biochim. Biophys. Acta **150:** 509–517, 1968.
753. LONG, T. T., JAKOI, L., STEVENS, R., AND QUARFORDT, S.: The sources of rat biliary cholesterol and bile acid. J. Lipid Res. **19:** 872–878, 1978.
754. LOUD, A. V.: A quantitative stereological description of the ultrastructure of normal rat liver parenchymal cells. J. Cell Biol. **37:** 27–46, 1968.
755. LUMENG, L., EDMONDSON, J. W., SCHENKER, S., AND LI, T.-K.: Transport and metabolism of thiamin in isolated rat hepatocytes. J. Biol. Chem. **254:** 7265–7268, 1979.
756. LUNZER, M. R., HUANG, S. N., WARD, K. M., AND SHERLOCK, S.: Jaundice due to erythromycin estolate. Gastroenterology **68:** 1284–1291, 1975.
757. LUPIANI, M., ZAMORA, S., ESTELLER, A., AND LOPEZ, M. A.: Effects of hypothermia on some aspects of biliary secretion in anaesthetized rabbits and rats. Comp. Biochem. Physiol. **64A:** 185–189, 1979.
758. LYKISSAS, E. D., KOUROUNAKIS, P., AND BROOKMAN, S.: Effect of pregenolone-16α-carbonitrile on bilirubin- and sulfobromophthalein-binding to hepatic Y and Z proteins in the rat. Pharmacology **16:** 217–220, 1978.
759. MACAROL, V., MORRIS, T. Q., BAKER, K. J., AND BRADLEY, S. E.: Hydrocortisone choleresis in the dog. J. Clin. Invest. **49:** 1714–1723, 1970.
760. MACLEOD, S. M., GILES, H. G., BENGERT, B., LIU, F. F., AND SELLERS, E. M.: Age- and gender-related differences in diazepam pharmacokinetics. J. Clin. Pharmacol. **19:** 15–19, 1979.
761. MACLEOD, S. M., RENTON, K. W., AND EADE, N. R.: Development of hepatic microsomal drug-oxidizing enzymes in immature male and female rats. J. Pharmacol. Exp. Ther. **183:** 489–498, 1972.
762. MADDREY, W., AND BOYER, J.: The acute and chronic effects of ethanol administration on bile secretion in the rat. J. Lab. Clin. Med. **82:** 215–225, 1973.
763. MAGOS, L., CLARKSON, T. W., AND ALLEN, J.: The interrelationship between non-protein bound thiols and the biliary excretion of methylmercury. Biochem. Pharmacol. **27:** 2203–2208, 1978.
764. MAGOS, L., CLARKSON, T. W., ALLEN, J., AND SNOWDEN, R.: The effects of bromosulphophthalein, indocyanine green and bilirubin on the biliary excretion of methylmercury. Chem.-Biol. Interact. **26:** 317–320, 1979.
765. MAHON, W. A., INABA, T., UMEBA, T., TSUTSUMI, E., AND STONE, R.: Biliary elimination of diazepam in man. Clin. Pharmacol. Ther. **19:** 443–450, 1976.
766. MAHU, J.-L., DUVALDESTIN, P., DHUMEAUX, D., AND BERTHELOT, P.: Biliary transport of cholephilic dyes: Evidence for two different pathways. Am. J. Physiol. **232:** E445–E450, 1977.
767. MAITRA, S. K., RACHMILEWITZ, D., EBERLE, D., AND KAPLOWITZ, N.: The hepatocellular uptake and biliary excretion of endotoxin in the rat. Hepatology **1:** 401–407, 1981.
768. MAKINO, I., AND NAKAGAWA, S.: Changes of biliary lipid and biliary bile acid composition in patients after administration of ursodeoxycholic acid. J. Lipid Res. **19:** 723–726, 1979.
769. MAKINO, I., NAKAGAWA, S., AND MASHIMO, K.: Conjugated and unconjugated serum bile acid levels in patients with hepatobiliary diseases. Gastroenterology **56:** 1033–1039, 1969.
770. MAKINO, I., SHINOZAKI, K., YOSHINO, K., AND NAKAGAWA, S.: Dissolution of cholesterol gallstones by ursodeoxycholic acid. Jpn. J. Gastroenterol. **72:** 690–702, 1975.
771. MALLET, L., FOLIOT, A., AMAT, D., PETITE, J.-P., HOUSSET, E., AND CAMILLERI, J.-P.: Cytochrome P-450 et bilirubine-glucuronosyl transferase hepatiques dans la cirrhose du rat au tetrachlorure de carbone: Demonstration d'une induction enzymatique par le clofibrate. Gastroenterol. Clin. Biol. **4:** 425–431, 1980.
772. MANNICK, M., AND AREND, W. P.: Fate of preformed immune complexes in rabbits and rhesus monkeys. J. Exp. Med. **134:** 19s–31s, 1971.
773. MANZATO, E., FELLIN, R., BAGGIO, G., WELCH, S., NEUBECK, W., AND SEIDEL, D.: Formation of lipoprotein. X. Its relationship to bile compounds. J. Clin. Invest. **57:** 1248–1260, 1976.
774. MARGOSHES, M., AND VALLEE, B. T.: A cadmium protein from equine kidney cortex. J. Am. Chem. Soc. **79:** 4813–4814, 1957.
775. MARKS, J. W., SHERMAN, J. H., BONORRIS, G. G., CHUNG, A., COYNE, M. J., AND SCHOENFIELD, L. J.: Gallstone dissolution by chenodeoxycholic acid and phenobarbital. Am. J. Gastroenterol. **69:** 160–165, 1978.
776. MARSHALL, T. C., AND DOROUGH, H. W.: Biliary excretion of carbamate insecticides in the rat. Pestic. Biochem. Physiol. **11:** 56–63, 1979.
777. MARZO, A., AND GHIRARDI, P.: Biliary and urinary excretion of five cardiac glycosides and its correlation with their physical and chemical properties. Naunyn-Schmiedeberg's Arch. Pharmacol. **298:** 51–56, 1977.
778. MASON, R.: Metabolism of cadmium in the neonate: Effect of hepatic zinc,

copper, and metallothionein concentrations on the uptake of cadmium in the rat liver. Biochem. Pharmacol. **31:** 1761–1764, 1982.
779. MATERN, S., AND GEROK, W.: Pathophysiology of the enterohepatic circulation. Rev. Physiol. Biochem. Pharmacol. **85:** 126–204, 1979.
780. MATON, P. N., MURPHY, G. M., AND DOWLING, R. H.: Ursodeoxycholic acid treatment of gallstones. Dose-response study and possible mechanism of action. Lancet **2:** 1297–1301, 1977.
781. MATSUI, M., AND HAKOZAKI, M.: Comparison of biliary metabolites of androsterone glucuronide and androsterone sulphate in female rats. J. Steroid Biochem. **8:** 1243–1248, 1977.
782. MATTER, A., ORCI, L., AND ROUILLER, C.: A study on the permeability barriers between Disse's space and the bile canaliculus. J. Ultrastruct. Res., suppl. 11, 5–71, 1969.
783. MATTHEWS, H. B.: Excretion of insecticides. Pharmacol. Ther. **4:** 657–675, 1979.
784. MCDEVITT, D. G., NIES, A. S., AND WILKINSON, G. R.: Influence of phenobarbital on factors responsible for hepatic clearance of indocyanine green in the rat: Relative contribution of induction and altered liver blood flow. Biochem. Pharmacol. **26:** 1247–1250, 1977.
785. MEHENDALE, H. M.: Effect of preexposure to kepone on the biliary excretion of imipramine and sulfobromophthalein. Toxicol. Appl. Pharmacol. **40:** 247–259, 1977.
786. MEHENDALE, H. M., HO, I. K., AND DESAIAH, D.: Possible molecular mechanism of mirex-induced hepatobiliary dysfunction. Drug Metab. Dispos. **7:** 28–33, 1979.
787. MEIJER, D. K. F.: The mechanisms for hepatic uptake and biliary excretion of organic cations. Excerpta Med. Int. Congr. Ser. **391:** 196–207, 1975.
788. MEIJER, D. K. F., ARENDS, J. W., AND WEITERING, J. G.: The cardiac glycoside sensitive step in the hepatic transport of the bisquaternary ammonium compound, hexaflourenium. Eur. J. Pharmacol. **15:** 245–251, 1971.
789. MEIJER, D. K. F., BLOM, A., AND WEITERING, J. G.: The influence of phenobarbital pretreatment on the subcellular distribution in liver and transport rate in isolated hepatocytes of dibromosulfophthalein. Biochem. Pharmacol. **31:** 2539–2542, 1982.
790. MEIJER, D. K. F., BOGNACKI, J., AND LEVINE, W. G.: Effect of nafenopin (SU-13,437) on liver function. Hepatic uptake and biliary excretion of ouabain in the rat. Drug Metab. Dispos. **3:** 220–225, 1975.
791. MEIJER, D. K. F., BOGNACKI, J., AND LEVINE, W. G.: Effect of nafenopin (SU-13,437) on liver function: Influence on the hepatic transport of organic anions. Naunyn-Schmiedeberg's Arch. Pharmacol. **290:** 235–250, 1975.
792. MEIJER, D. K. F., BOS, E. S., AND VAN DER LAAN, K. J.: Hepatic transport of mono and bisquaternary ammonium compounds. Eur. J. Pharmacol. **11:** 371–377, 1970.
793. MEIJER, D. K. F., VERMEER, G. A., AND KWANT, G.: The excretion of hexaflourenium in man and rat. Eur. J. Pharmacol. **14:** 280–285, 1971.
794. MEIJER, D. K. F., VONK, R. J., KEULEMANS, K., AND WEITERING, J. G.: Hepatic uptake and biliary excretion of dibromosulphthalein. Albumin dependence, influence of phenobarbital and nafenopin pretreatment and the role of Y and Z protein. J. Pharmacol. Exp. Ther. **202:** 8–21, 1977.
795. MEIJER, D. K. F., VONK, R. J., SCHOLTENS, E. J., AND LEVINE, W. G.: The influence of dehydrocholate on hepatic uptake and biliary excretion of ^{3}H-taurocholate and ^{3}H-ouabain. Drug Metab. Dispos. **4:** 1–7, 1976.
796. MEIJER, D. K. F., VONK, R. J., AND WEITERING, J. G.: The influence of various bile salts and some cholephilic dyes on Na^{+}, K^{+}- and Mg^{++}-activated ATPase of rat liver in relation to cholestatic effects. Toxicol. Appl. Pharmacól. **43:** 597–612, 1978.
797. MEIJER, D. K. F., WEITERING, J. G., AND VONK, R. J.: Hepatic uptake and biliary excretion of *d*-tubocurarine and trimethyltubocurarine in the rat in vivo and in isolated perfused rat livers. J. Pharmacol. Exp. Ther. **198:** 229–239, 1976.
798. MEIJER, D. K. F., WESTER, J., AND GUNNINK, M.: Distribution of quaternary ammonium compounds between particulate and soluble constituents of rat liver, in relation to their transport from plasma into bile. Naunyn-Schmiedeberg's Arch. Pharmacol. **273:** 179–192, 1972.
799. MEINERTZ, T., GILFRISH, H., GROTH, U., JOEN, H. G., AND JAHNCHEN, E.: Interruption of the enterohepatic circulation of phenprocoumon by cholestyramine. Clin. Pharmacol. Ther. **21:** 731–735, 1977.
800. MAKHJIAN, S. H., PHILLIPS, S. F., AND HOFMANN, A. F.: Colonic absorption of unconjugated bile acids. Perfusion studies in man. Am. J. Dig. Dis. **24:** 545–550, 1979.
801. MERLE, L., DANGOUMAU, J., AND BALABAUD, C.: Effect of food and light schedule on bile flow in the rat. Experientia (Basel) **34:** 764–765, 1978.
802. METHFESSEL, A. H., AND SPENCER, H.: Zinc metabolism in the rat. II. Secretion of zinc into intestine. J. Appl. Physiol. **34:** 63–67, 1973.
803. METZ, J., AND BRESSLER, D.: Reformation of gap and tight junctions in regenerating liver after cholestasis. Cell. Tissue Res. **199:** 257–270, 1979.
804. MEYERS, M., SLIKKER, W., PASCOE, G., AND VORE, M.: Characterization of cholestasis induced by estradiol-17β-D-glucuronide in the rat. J. Pharmacol. Exp. Ther. **214:** 87–93, 1980.
805. MEYERS, M., SLIKKER, W., AND VORE, M.: Steroid D-ring glucuronides: Characterization of a new class of cholestatic agents in the rat. J. Pharmacol. Exp. Ther. **218:** 63–73, 1981.
806. MEYERS, W. C., HANKS, J. B., AND JONES, R. C.: Inhibition of basal and meal-stimulated choleresis by somatostatin. Surgery **86:** 301–306, 1979.
807. MIGUET, J.-P., MAVIER, P., ARONDEL, J., PREAUX, A.-M., AND DHUMEAUX, D.: Effet de la spironolactone sur la cholerese et les enzymes microsomales hepatiques du rat. Gastroenterol. Clin. Biol. **1:** 1007–1013, 1977.
808. MILLBURN, P., SMITH, R. L., AND WILLIAMS, R. T.: Biliary excretion of foreign compounds; biphenyl, stilboesterol and phenolphthalein in the rat: Molecular weight, polarity and metabolism as factors in biliary excretion. Biochem. J. **105:** 1275–1281, 1967.
809. MILLBURN, P., SMITH, R. L., AND WILLIAMS, R. T.: Biliary excretion of foreign compounds; sulphonamide drugs in the rat. Biochem. J. **105:** 1283–1287, 1967.
810. MILLER, E. B., SORSCHER, A., AND SPENCER, H.: Intestinal Zn^{65} secretion in man. Radiat. Res. **22:** 216–217, 1964.
811. MINER, P. B., JR., AND GAITO, J. M.: Bile flow in response to pharmacologic agents. Biochem. Pharmacol. **28:** 1063–1066, 1979.
812. MIYAI, K., AND HARDISON, W. G. M.: Cholestasis induced by scillaren administration, bicarbonate deprivation, or reduced hepatic blood flow. Exp. Mol. Pathol. **36:** 333–346, 1982.
813. MIYAI, K., RICHARDSON, A. L., MAYR, W., AND JAVITT, N. B.: Subcellular pathology of rat liver in cholestasis and choleresis induced by bile salts. I. Effect of lithocholic, 3-beta-hydroxy-5-cholenoic, cholic and dehydrocholic acids. Lab. Invest. **36:** 249–258, 1977.
814. MIYAZAKI, T., MIZUKOSHI, H., AND ARAKI, Y.: Biliary and urinary metabolites of estrone in the guinea pig. J. Steroid Biochem. **9:** 115–119, 1978.
815. MIZOGUCHI, Y., TAKASHI, S., FUMIAKI, O., TAKEYUKI, M., SUKEO, Y., AND SEIJI, M.: Immunological studies on the drug-induced allergic hepatitis. Gastroenterol. Jpn. **16:** 249–259, 1981.
816. MOK, H. Y. I., VON BERGMANN, K., AND GRUNDY, S. M.: Regulation of pool size of bile acids in man. Gastroenterology **73:** 684–690, 1977.
817. MONTGOMERY, C., AND VORE, M.: The effect of diethylstilbesterol treatment on the metabolism and biliary excretion of [^{14}C]phenytoin in the isolated perfused rat liver. Toxicol. Appl. Pharmacol. **58:** 510–519, 1981.
818. MONTGOMERY, C. L., VORE, M., SCHLARMAN, D., AND ELLIOTT, W. H.: Structure activity relationship of the cholestatic activity of all bile acids, lithocholate, and dihydrotestosterone glucuronide. Fed. Proc. **42:** 757, 1983.
819. MOSS, A., LIN, S., AND RIEGELMAN, S.: Pharmacokinetics of iopanoate and indoxamate in rhesus monkeys. Invest. Radiol. **15:** S132–S135, 1980.
820. MROSZCZAK, E. J., AND RIEGELMAN, S.: Biliary excretion of diethylstilbestrol in the rhesus monkey. J. Pharmacokinet. Biopharm. **6:** 339–354, 1978.
821. MUELLER, M. N., AND KAPPAS, A.: Estrogen pharmacology. I. The influence of estradiol and estriol on hepatic disposal of sulfobromophthalein (BSP) in man. J. Clin. Invest. **43:** 1905–1914, 1964.
822. MULLER, W., AND STILLBAUER, A. E.: Liver slice uptake of intravenous and oral biliary contrast media. Arch. Int. Pharmacodyn. Ther. **246:** 187–204, 1980.
823. MULLER, W. E., AND STILLBAUER, A. E.: Biliary contrast agents: Comparative study about the binding to human plasma and the effect of human plasma on hepatic uptake. Pharmacology **22:** 269–275, 1981.
824. MULLOCK, B., DOBROTA, M., AND HINTON, R.: Sources of protein in rat bile. Biochim. Biophys. Acta **543:** 497–507, 1978.
825. MULLOCK, B. M., AND HINTON, R. H.: Mechanisms by which newly made glycoproteins are transferred from hepatocytes into bile. FEBS Lett. **106:** 121–124, 1979.
826. MULLOCK, B. M., AND HINTON, R. H.: Transport of proteins from blood to bile. Trends Biomed. Sci. **6:** 188–190, 1981.
827. MULLOCK, B. M., HINTON, R. H., DOBROTA, M., PEPPARD, J., AND ORLANS, E.: Endocytic vesicles in liver carry polymeric IgA from serum to bile. Biochim. Biophys. Acta **587:** 381–391, 1979.
828. MULLOCK, B., HINTON, R., DOBROTA, M., PEPPARD, J., AND ORLANS, E.: Distribution of secretory component in hepatocytes and its mode of transfer into bile. Biochem. J. **190:** 819–826, 1980.
829. MULLOCK, B. M., JONES, R. S., AND HINTON, R. H.: Movement of endocytic shuttle vesicles from the sinusoidal to the bile canalicular face of hepatocytes does not depend on occupation of receptor sites. FEBS Lett. **113:** 201–205, 1980.
830. MURPHY, P. J., WILLIAMS, T. L., MCMAHON, R. E., CRABTREE, R. E., AND RIDOLFO, A. S.: Metabolism of propionyl erythromycin lauryl sulfate. II. Fate of the lauryl sulfate moiety in the rat and man. Drug Metab. Dispos. **3:** 164–170, 1975.
831. MURPHY, P. J., WILLIAMS, T. L., MCMAHON, R. E., AND MARSHALL, F. J.: Metabolism of propionyl erythromycin lauryl sulfate. I. Fate of the propionyl erythromycin moiety in the rat. Drug Metab. Dispos. **3:** 155–163, 1975.
832. NAHRWOLD, D. L.: Secretion by the common duct in response to secretin. Surg. Forum **22:** 386–387, 1971.
833. NAKAE, H., IUCHI, Y., AND MURANISHI, S.: Biopharmaceutical study of the hepato-biliary transport of drugs. VIII. Investigation of hepatic uptake of organic cations by portal infusion. Chem. Pharm. Bull. (Tokyo) **26:** 88–95, 1978.
834. NAKAE, H., MURANISHI, S., ASADA, S., AND TAKADA, K.: Pharmacokinetic

study on saturated hepato-biliary transport of acetyl procainamide ethobromide. J. Pharm. Dyn. **4:** 584–589, 1981.

835. NAKAE, H., SAKATA, R., AND MURANISHI, S.: Biopharmaceutical study of the hepato-biliary transport of drugs. V. Hepatic uptake and biliary excretion of organic cations. Chem. Pharm. Bull. (Tokyo) **24:** 886–893, 1976.
836. NAKAE, H., TAKADA, K., ASADA, S., AND MURANISHI, S.: Use of a fluorescent sulfhydryl reagent, N-[*p*-(2-benzimidazolyl)phenyl] maleimide, in investigating active biliary excretion of organic cations. J. Pharm. Dyn. **2:** 19–26, 1979.
837. NAKAE, H., TAKADA, K., ASADA, S., AND MURANISHI, S.: Transport rates of hepatic uptake and biliary excretion of an organic cation, acetyl procainamide ethobromide. Biochem. Pharmacol. **29:** 2573–2576, 1980.
838. NAKATSUGAWA, T., BRADFORD, W., AND USUI, K.: Hepatic disposition of parathion: Uptake by isolated hepatocytes and chromatographic translobular migration. Pest. Biochem. Physiol. **14:** 13–25, 1980.
839. NAYAK, P. K., AND SCHANKER, L. S.: Active transport of tertiary amine compounds into bile. Am. J. Physiol. **217:** 1639–1643, 1969.
840. NEALE, M. G., AND PARKE, D. V.: Effects of pregnancy on the metabolism of drugs in the rat and rabbit. Biochem. Pharmacol. **22:** 1451–1461, 1973.
841. NEEDLEMAN, P., LANG, S., AND JOHNSON, E. M., JR.: Organic nitrates: Relationship between biotransformation and rational angina pectoris therapy. J. Pharmacol. Exp. Ther. **181:** 489–497, 1972.
842. NEEF, K., JONKMAN, J. H. G., AND MEIJER, D. K. F.: Hepatic disposition and biliary excretion of the organic cations thiazinamium and thiazinamium sulfoxide in rats. J. Pharm. Sci. **67:** 1147–1150, 1978.
843. NEIDERHISER, D. H., ROTH, H. P., AND WEBSTER, L. T., JR.: Studies on the importance of lecithin for cholesterol solubilization in bile. J. Lab. Clin. Med. **68:** 90–102, 1966.
844. NEMCHAUSKY, B. A., LAYDEN, T. J., AND BOYER, J. L.: Effects of chronic choleretic infusion of bile acids on the membrane of the bile canaliculus. Lab. Invest. **36:** 259–267, 1977.
845. NEUFELD, E., AND ASHWELL, G.: Carbohydrate recognition systems for receptor-mediated pinocytosis. *In* Biochemistry of Glycoproteins and Proteoglycans, ed. by W. Lennarz, pp. 241–266, Plenum Press, New York, 1979.
846. NEUMANN, K. H., AND RECTOR, F. C., JR.: Mechanism of NaCl and water reabsorption in the proximal convoluted tubule of rat kidney. J. Clin. Invest. **58:** 1110–1118, 1976.
847. NEUVONEN, P. J., AND ELONEN, E.: Effect of activated charcoal on absorption and elimination of phenobarbitone, carbamazepine and phenylbutazone in man. Eur. J. Clin. Pharmacol. **17:** 51–57, 1980.
848. NEXO, E., AND HOLLENBERG, M. D.: Characterization of the particulate and soluble acceptor for transcobalamin II from human placenta and rabbit liver. Biochim. Biophys. Acta **628:** 190–200, 1980.
849. NICOLAU, G., SHEFER, S., SALEN, G.: Determination of hepatic 3-hydroxy-3-methylglutaryl CoA reductase activity in man. J. Lipid Res. **15:** 94–98, 1974.
850. NIES, A. S., WILKINSON, G. R., RUSH, B. D., STROTHER, J. T., AND MCDEVITT, D. G.: Effects of alteration of hepatic microsomal enzyme activity on liver blood flow in the rat. Biochem. Pharmacol. **25:** 1991–1993, 1976.
851. NIES, A. S., SHAND, D. G., AND WILKINSON, G. R.: Altered hepatic blood flow and drug disposition. Clin. Pharmacokin. **1:** 135–155, 1976.
852. NILSSON, H., PERSSON, C., TEGNER, K., INGEMARSSON, I., AND LIEDBERG, G.: Biliary excretion of ^{3}H-terbutaline in man. Biochem. Pharmacol. **22:** 3128–3129, 1973.
853. NILSSON, S., AND SCHERSTEN, T.: Importance of bile acids for phospholipid secretion into human hepatic bile. Gastroenterology **57:** 525–532, 1969.
854. NOLAN, J. P.: Endotoxin, reticuloendothelial function and liver injury. Hepatology **1:** 458–465, 1981.
855. NORDBERG, G., NORDBERG, M., PISCATOR, M., AND VESTERBERG, O.: Separation of two forms of rabbit metallothionein by isoelectric focusing. Biochem. J. **126:** 491–498, 1972.
856. NORTHFIELD, T. C., AND HOFMANN, A. F.: Biliary lipid secretion in gallstone patients. Lancet **1:** 747–748, 1973.
857. NORSETH, T.: Biliary excretion and intestinal reabsorption of mercury in the rat after injection of methyl mercuric cloride. Acta Pharmacol. Toxicol. **33:** 280–288, 1973.
858. NORSETH, T., AND CLARKSON, T. W.: Intestinal transport of ^{203}Hg-labeled methyl mercury chloride: Role of biotransformation in rats. Arch. Environ. Health **22:** 568–577, 1971.
859. NOVIKOFF, A. B.: Cell heterogeneity within the hepatic lobule of the rat (staining reactions). J. Histochem. Cytochem. **7:** 240–244, 1959.
860. OCHS, H. R., CARSTENS, G., AND GREENBLATT, D. J.: Reduction in lidocaine clearance during continuous infusion and by coadministration of propranolol. N. Engl. J. Med. **303:** 373–377, 1980.
861. OCKNER, R. K., AND DAVIDSON, C. S.: Hepatic effects of oral contraceptives. N. Engl. J. Med. **276:** 331–334, 1967.
862. ODA, M., PRICE, V. M., FISCHER, M. M., AND PHILLIPS, M. J.: Ultrastructure of bile canaliculi with special reference to the surface coat of the pericanalicular web. Lab. Invest. **31:** 314–323, 1974.
863. OGAWA, E., SUZUKI, S., AND TSUZUKI, H.: Radiopharmacological studies on the cadmium poisoning. Jpn. J. Pharmacol. **22:** 275–281, 1972.
864. OGUMA, T., AND LEVY, G.: Acute effect of ethanol on hepatic first-pass elimination of propoxyphene in rats. J. Pharmacol. Exp. Ther. **219:** 7–13, 1981.
865. OH, S. H., DEAGEN, J. T., WHANGER, P. D., AND WESWIG, P. H.: Biological function of metallothionein. V. Its induction in rats by various stresses. Am. J. Physiol. **234:** E282–E285, 1978.
866. OHKUBO, H., OKUDA, K., AND IIDA, S.: Effects of corticosteroids on bilirubin metabolism in patients with Gilbert's syndrome. Hepatology **1:** 168–172, 1981.
867. OHNHAUS, E. E., THORGEIRSSON, S. S., DAVIS, D. S., AND BRECKENRIDGE, A.: Changes in liver blood flow during enzyme induction. Biochem. Pharmacol. **20:** 2561–2570, 1971.
868. OHNHAUS, E. E., AND TILVIS, R.: Liver blood flow, metabolic heat production and body temperature before, during the after phenobarbitone administration. Acta Hepato-Gastroenterol. **23:** 404–408, 1976.
869. OKITA, G. T., TALSO, P. J., CURRY, J. H., JR., SMITH, F. D., JR., AND GEILING, E. M. K.: Metabolic fate of radioactive digitoxin in human subjects. J. Pharmacol. Exp. Ther. **115:** 371–379, 1955.
870. OKOLICSANYI, L., ORLANDO, R., VENUTI, M., DAL BRUN, G., COBELLI, C., RUGGERI, A., AND SALVAN, A.: A modeling study of the effect of fasting on bilirubin kinetics in Gilbert's syndrome. Am. J. Physiol. **240:** R266–R271, 1981.
871. OLIVECRONA, T., AND SJOVALL, J.: Bile acids in rat portal blood. Bile acids and steroids 77. Acta Physiol. Scand. **46:** 284–290, 1959.
872. OLSON, J. R., AND FUJIMOTO, J. M.: Demonstration of a D-glucose transport system in the biliary tree of the rat by use of the segmented retrograde intrabiliary injection technique. Biochem. Pharmacol. **29:** 213–219, 1980.
873. OLSON, J. R., AND FUJIMOTO, J. M.: Evaluation of hepatobiliary function in the rat by the segmented retrograde intrabiliary injection technique. Biochem. Pharmacol. **29:** 205–211, 1980.
874. OLSON, J. R., HOSKO, M. J., AND FUJIMOTO, J. M.: Alterations in the liver cell transmembrane potential following CCl_4 and bile salt treatment of rats. Life Sci. **25:** 2043–2050, 1979.
875. O'MAILLE, E. R. L.: The influence of micelle formation on bile salt secretion. J. Physiol. **302:** 107–120, 1980.
876. O'MAILLE, E. R., AND RICHARDS, T. G.: The secretory characteristics of dehydrocholate in the dog: Comparison with the natural bile salts. J. Physiol. (Lond.) **261:** 337–357, 1976.
877. O'MAILLE, E. R. L., AND RICHARDS, T. G.: Possible explanations for the differences in secretory characteristics between conjugated and free bile acids. J. Physiol. (Lond.) **265:** 855–866, 1977.
878. O'MAILLE, E. R. L., RICHARDS, T. G., AND SHORT, A. H.: Factors determining the maximal rate of organic anion secretion by the liver and further evidence on the hepatic site of action of the hormone secretin. J. Physiol. (Lond.) **186:** 424–438, 1966.
879. O'MAILLE, E. R. L., RICHARDS, T. G., AND SHORT, A. H.: The influence of conjugation of cholic acid on its uptake and secretion: Hepatic extraction of taurocholate and cholate in the dog. J. Physiol. (Lond.) **189:** 337–350, 1967.
880. OMATA, S., SAKIMURA, K., ISHII, T., AND SUGANO, H.: Chemical nature of a methylmercury complex with a low molecular weight in the liver cytosol of rats exposed to methylmercury chloride. Biochem. Pharmacol. **27:** 1700–1701, 1978.
881. ONISKO, B. L., ESVELT, R. P., SCHNOES, H. K., AND DELUCA, H. F.: Excretion of metabolites of 1α,25-dihydroxyvitamin D_3 in rat bile. Arch. Biochem. Biophys. **205:** 175–179, 1980.
882. O'REILLY, S., WEBER, P. M., OSWALD, M., AND SHIPLEY, L.: Abnormalities of the physiology of copper in Wilson's disease. III. The excretion of copper. Arch. Neurol. **25:** 28–32, 1971.
883. ORLANS, E., PEPPARD, J., FRY, J., HINTON, R. H., AND MULLOCK, B. M.: Secretory component as the receptor for polymeric IgA on rat hepatocytes. J. Exp. Med. **150:** 1577–1581, 1979.
884. ORLANS, E., PEPPARD, J., REYNOLDS, J., AND HALL, J.: Rapid active transport of immunoglobulin A from blood to bile. J. Exp. Med. **147:** 588–592, 1978.
885. ORLOFF, J., AND HANDLER, J.: The role of adenosine 3′,5′-phosphate in the action of antidiuretic hormone. Am. J. Med. **42:** 757, 1967.
886. OSE, L., OSE, T., NORUM, K. R., AND BERG, T.: Uptake and degradation of ^{125}I-labeled high density lipoproteins in rat liver cells in vivo and in vitro. Biochim. Biophys. Acta **574:** 521–536, 1979.
887. OSUGA, T.: Bile secretion. Drug Metab. Dispos. **12:** 1121–1127, 1975.
888. OWEN, C. A., JR.: Absorption and excretion of ^{64}Cu-labeled copper by the rat. Am. J. Physiol. **207:** 1203–1206, 1964.
889. OWEN, C. A.: Isolated rat liver needs calcium to make bile. Proc. Soc. Exp. Biol. Med. **155:** 314–317, 1977.
890. OWEN, C. A., AND HAZELRIG, J. B.: Metabolism of Cu^{64}-labeled copper by the isolated rat liver. Am. J. Physiol. **210:** 1059–1064, 1966.
891. OWEN, C. A., AND ORVIS, A. L.: Release of copper by rat liver. Am. J. Physiol. **218:** 88–91, 1970.
892. PALMER, R. H.: Toxic effects of lithocholic acid and related 5-β-H-steroids. *In* Bile Salt Metabolism, ed. by L. Schiff, J. B. Carey, Jr., and J. M. Dietschy, pp. 184–204, Charles C Thomas, Springfield, IL, 1969.

893. PANG, K. S., AND GILLETTE, J. R.: Sequential first-pass elimination of a metabolite derived from a precursor. J. Pharmacokinet. Biopharm. 7: 275–290, 1979.

894. PANG, K. S., AND ROWLAND, M.: Hepatic clearance of drugs. I. Theoretical considerations of a "well-stirred" model and a "parallel tube" model. Influence of hepatic blood flow, plasma and blood cell binding, and the hepatocellular enzymatic activity on hepatic drug clearance. J. Pharmacokinet. Biopharm. 5: 625–653, 1977.

895. PANG, K. S., AND ROWLAND, M.: Hepatic clearance of drugs. II. Experimental evidence for acceptance of the "well-stirred" model over the "parallel tube" model using lidocaine in the perfused rat liver in situ preparation. J. Pharmacokinet. Biopharm. 5: 655–680, 1977.

896. Pang, K. S., and Rowland, M.: Hepatic clearance of drugs. III. Additional experimental evidence supporting the "well-stirred" model, using metabolite (MEGX) generated from lidocaine under varying hepatic blood flow rates and linear conditions in the perfused rat liver in situ preparation. J. Pharmacokinet. Biopharm. 5: 681–699, 1977.

897. PARDRIDGE, W. M., AND JEFFERSON, L. S.: Liver uptake of amino acids and carbohydrates during a single circulatory passage. Am. J. Physiol. 228: 1155–1161, 1975.

898. PARKER, R. J., HIROM, P. C., AND MILLBURN, P.: Enterohepatic recycling of phenolphthalein, morphine, lysergic acid diethylamide (LSD) and diphenylacetic acid in the rat: Hydrolysis of glucuronic-acid conjugates in the gut lumen. Xenobiotica 10: 689–703, 1980.

899. PAUMGARTNER, G.: The handling of indocyanine green by the liver. Schweiz. Med. Wochenschr. (suppl.) 105: 1–30, 1975.

900. PAUMGARTNER, G., HORAK, W., PROBST, P., AND GRABNER, G.: Effect of phenobarbital on bile flow and bile salt excretion in the rat. Naunyn-Schmeideberg's Arch. Pharmakol. 270: 98–101, 1971.

901. PAUMGARTNER, G., PROBST, P., KRAINES, R., AND LEEVY, C. M.: Kinetics of indocyanine green removal from the blood. Ann. N.Y. Acad. Sci. 170: 134–142, 1970.

902. PAUMGARTNER, G., AND REICHEN, J.: Different pathways for hepatic uptake of taurocholate and indocyanine green. Experientia (Basel) 31: 306–308, 1975.

903. PAUMGARTNER, G., AND REICHEN, J.: Kinetics of hepatic uptake of unconjugated bilirubin. Clin. Sci. Mol. Med. 51: 169–176, 1976.

904. PAUMGARTNER, G., SAUTER, K., SCHWARZ, H. P., AND HERZ, R.: Hepatic excretory transport maximum for free and conjugated cholate in the rat. *In* The Liver: Quantitative Aspects of Structure and Function, ed. by G. Paumgartner and R. Preisig, pp. 337–344, Karger, Basel, 1973.

905. PEREZ, V., SCHAFFNER, F., AND POPPER, H.: Hepatic drug reactions. *In* Progress in Liver Disease, ed. by H. Popper and F. Schaffner, vol. 4, pp. 597–625, Grune & Stratton, New York, 1972.

906. PERRIER, D., AND GIBALDI, M.: Influence of first-pass effect on the systemic availability of propoxyphene. J. Clin. Pharmacol. 12: 449–452, 1972.

907. PESSAYRE, D., LEBREC, D., DESCATOIRE, V., PEIGNOUX, M., AND BENHAMOU, J. P.: Mechanism for reduced drug clearance in patients with cirrhosis. Gastroenterology 74: 566–571, 1978.

908. PETERLIK, M., AND GAZDA, H.: Sodium-linked transport of ethacrynic acid by rat liver: Possible significance for choleretic action. Biochem. Pharmacol. 29: 2733–2739, 1980.

909. PETERSON, R. E.: Retrodifferentiation: A mechanism for the depression of ouabain biliary excretion in the male rats treated with 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. *In* Toxicology of Halogenated Hydrocarbons: Health and Ecological Effects, ed. by M. A. Q. Kahn and R. H. Stanton, pp. 133–145, Pergamon Press, New York, 1981.

910. PETERSON, R. E., AND FUJIMOTO, J. M.: Biliary excretion of morphine-3-glucuronide and morphine-3-ethereal sulfate by different pathways in the rat. J. Pharmacol. Exp. Ther. 184: 409–418, 1973.

911. PETERSON, R. E., AND FUJIMOTO, J. M.: Retrograde intrabiliary injection: Absorption of water and other compounds from the rat biliary tree. J. Pharmacol. Exp. Ther. 185: 150–162, 1973.

912. PETERSON, R. E., AND FUJIMOTO, J. M.: A study of absorption of compounds from the rat biliary tree by retrograde intrabiliary injection (RII). J. Pharmacol. Exp. Ther. 194: 126–134, 1975.

913. PETERSON, R. E., AND FUJIMOTO, J. M.: Increased biliary tree permeability produced in rats by hepatoactive agents. J. Pharmacol. Exp. Ther. 202: 732–739, 1977.

914. PETERSON, R. E., HAMADA, N., YANG, K. H., MADHUKAR, B. V., AND MATSUMURA, F.: Reversal of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin-induced depression of ouabain biliary excretion by pregnenolone-16α-carbonitrile and spironolactone in isolated perfused rat livers. Toxicol. Appl. Pharmacol. 50: 407–416, 1979.

915. PETERSON, R. E., MADHUKAR, B. V., YANG, K. H., AND MATSUMURA, F.: Depression of adenosine triphosphatase activities in isolated liver surface membranes of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin-treated rats: Correlation with effects on ouabain biliary excretion and bile flow. J. Pharmacol. Exp. Ther. 210: 275–282, 1979.

916. PETZINGER, E.: Competitive inhibition of the uptake of demethylphalloin by cholic acid in isolated hepatocytes. Evidence for a transport competition rather than a binding competition. Naunyn-Schmiedeberg's Arch. Pharmacol. 316: 345–349, 1981.

917. PETZINGER, E., AND FRIMMER, M.: Comparative studies on the uptake of ^{14}C-bile acids and ^{3}H-demethylphalloin in isolated rat liver cells. Arch. Toxicol. 44: 127–135, 1980.

918. PETZINGER, E., ZIEGLER, K., AND FRIMMER, M.: Inhibition of ^{3}H-demethylphalloin uptake in isolated rat hepatocytes under various experimental conditions. Naunyn-Schmiedeberg's Arch. Pharmacol. 307: 275–281, 1979.

919. PHILLIPS, M. J., ODA, M., MAK, E., FISHER, M. M., AND JEEJEEBHOY, K. N.: Microfilament dysfunction as a possible cause of intrahepatic cholestasis. Gastroenterology 69: 48–58, 1975.

920. PHILLIPS, M. J., OSHIO, C., MIYAIRI, M., KATZ, H., AND SMITH, C. R.: A study of bile canalicular contractions in isolated hepatocytes. Hepatology 2: 763–768, 1982.

921. PIERON, R., MARIEN, CL., AND JAGUEUX, M.: Icteres et rifampicine. Sem. Hop. Paris. 47: 1286–1295, 1971.

922. PIETRAS, R. J., AND SZEGO, C. M.: Partial purification and characterization of estrogen receptors in subfractions of hepatocyte plasma membranes. Biochem. J. 191: 743–760, 1980.

923. PIRTTIAHO, H. I., SOTANIEMI, E. A., PELKONEN, R. O., PITKANEN, U., ANTTILA, M., AND SUNDQUIST, H.: Roles of hepatic blood flow and enzyme activity in the kinetics of propranolol and sotalol. Br. J. Clin. Pharmacol. 9: 399–405, 1980.

924. PISSIDIS, A. G., NYHUS, I. M., AND BOMBECK, C. T.: Neurohumoral control of bile secretion in the cholecystectomized, conscious dog. Surgery 74: 122–129, 1973.

925. PLAA, G. L.: Functional aspects of the cholestatic response induced by α-naphthylisothiocyanate in mice and rats. Agents Actions 1: 22–27, 1969.

926. PLAA, G. L.: The enterohepatic circulation. *In* Handbook of Experimental Pharmacology, ed. by J. R. Gillette, and J. R. Mitchell, pp. 130–149, Springer-Verlag, Berlin-Heidelberg, 1975.

927. PLAA, G. L.: Nonsteroid drug-induced cholestasis and experimental cholestasis. *In* Jaundice, ed. by C. A. Goresky and M. M. Fischer, pp. 351–366, Plenum Press, New York, 1975.

928. PLAA, G. L., AND PRIESTLY, B. G.: Intrahepatic cholestasis induced by drugs and chemcials. Pharmacol. Rev. 28: 207–273, 1976.

929. PLAA, G. L., ROGERS, L. A., AND FOUTS, J. R.: Effect of acute alpha-naphthylisothiocyanate administration on hepatic microsomal drug metabolism in the mouse. Proc. Soc. Exp. Biol. Med. 119: 1045–1048, 1965.

930. POMARE, E. W., AND HEATON, K. W.: Alteration of bile salt metabolism by dietary fibre (bran). Br. Med. J. 4: 262–264, 1973.

931. POPPER, H.: Cholestasis. Annu. Rev. Med. 19: 39–56, 1968.

932. POPPER, H.: Cholestasis: The future of a past and present riddle. Hepatology 1: 187–191, 1981.

933. POUPON, R. E., DOL, M.-L., DUMONT, M., AND ERLINGER, S.: Evidence against a physiological role of cAMP in choleresis in dogs and rats. Biochem. Pharmacol. 27: 2413–2416, 1978.

934. POUPON, R. E., AND EVANS, W. H.: Biochemical evidence that Na^+, K^+-ATPase is located at the lateral region of the hepatocyte surface membrane. FEBS Lett. 108: 374–378, 1979.

935. POUPON, R. E., LEQUERNEC, L., MAURICE, M., AND ERLINGER, S.: Lack of effect of phenobarbital on bile flow and Na^+-K^+-ATPase activity of liver plasma membranes in the hamster. Gastroenterol. Chem. Biol. 5: 604–610, 1981.

936. Poupon, R. R., Poupon, R. Y., Dumont, M., and Erlinger, S.: Hepatic storage and biliary transport maximum of taurocholate and taurochenodeoxycholate in the dog. Eur. J. Clin. Invest. 6: 431–437, 1976.

937. POUPON, R. E., ROSENSZTAJN, L., PRUDHOMME DESAINT-MAUR, P., LAGERON, A., GOMBEAU, T., AND DARNIS, F.: Perhexiline maleate-associated hepatic injury prevalence and characteristics. Digestion 20: 145–150, 1980.

938. PRANDI, D., ERLINGER, S., GLASINOVIC, J.-C., AND DUMONT, M.: Canalicular bile production in man. Eur. J. Clin. Invest. 5: 1–6, 1975.

939. PREISIG, R.: *In* Liver and Drugs, ed. by F. Orlandi and A. M. Jezequel, chapt. 4, Academic Press, New York, 1972.

940. PREISIG, R., COOPER, H. L., AND WHEELER, H. O.: The relationship between taurocholate secretion rate and bile production in the unanesthetized dog during cholinergic blockade and during secretin administration. J. Clin. Invest. 41: 1152–1162, 1962.

941. PREISIG, R., STREBEL, H., EGGER, G., AND MACAROL, V.: Effect of vasopressin on hepatocytic and ductal bile formation in the dog. Experientia (Basel) 28: 1436–1437, 1972.

942. PRENTKI, M., CRETTAZ, M., AND JEANRENAUD, B.: A possible complementary role of actin microfilaments and microtubules in triacylglycerol secretion by isolated hepatocytes. Biochim. Biophys. Acta 627: 262–269, 1980.

943. PRIES, J. M., SHERMAN, C. A., WILLIAMS, G. C., AND HANSON, R. F.: Hepatic extraction of bile salts in conscious dog. Am. J. Physiol. 236: E191–E197, 1979.

944. PRIESTLY, B. G., COTE, M. G., AND PLAA, G. L.: Biochemical and morphological parameters of taurolithocholate-induced cholestasis. Can. J. Physiol. Pharmacol. 49: 1078–1091, 1971.

945. PRIESTLY, B. G., AND PLAA, G. L.: Effects of benziodarone on the metabolism and biliary excretion of sulfobromophthalein and related dyes. Proc. Soc. Exp. Biol. Med. 132: 881–885, 1969.

946. PRIESTLY, B. G., AND PLAA, G. L.: Sulfobromophthalein metabolism and

excretion in rats with iodomethane-induced depletion of hepatic glutathione. J. Pharmacol. Exp. Ther. **174:** 221–231, 1970.

947. PRIESTLY, B. G., AND PLAA, G. L.: Temporal aspects of carbon tetrachloride-induced alteration of sulfobromophthalein excretion and metabolism. Toxicol. Appl. Pharmacol. **17:** 786–794, 1970.
948. PRIESTLY, B. G., AND PLAA, G. L.: Reduced bile flow after sulfobromophthalein administration in the rat. Proc. Soc. Exp. Biol. Med. **135:** 373–376, 1970.
949. PRITCHARD, J. B., ANDERSON, J. B., RALL, D. P., AND GUARINO, A. M.: Comparative hepatic and renal handling of phenol red and indocyanine green by cyclostome, elasmobranch and teleost fish. Comp. Biochem. Physiol. **65C:** 99–104, 1980.
950. PUCHINGER, H., AND WIELAND, TH.: Suche nach einem metaboliten bei vergiftung mit desmethylphalloin (DMP). Eur. J. Biochem. **11:** 1–6, 1969.
951. PUGH, P. M., AND STONE, S. L.: The ionic composition of bile. J. Physiol. **201:** 508, 1969.
952. RADZIALOWSKI, F. M.: Effect of spironolactone and pregnenolone-16α-carbonitrile on bilirubin metabolism and plasma levels in male and female rats. Biochem. Pharmacol. **22:** 1607–1611, 1973.
953. RAMADORI, G., HOPF, U., AND MEYER ZUM BUSCHENFELDE, K. H.: Binding sites for endotoxic lipopolysaccharide on the plasma membrane of isolated rabbit hepatocytes. Acta Hepato-Gastroenterol. **26:** 368–374, 1979.
954. RAO, M. L., RAO, G. S., AND BREUR, H.: Uptake of estrone, estradiol-17β and testosterone by isolated rat liver cells. Biochem. Biophys. Res. Commun. **77:** 566–573, 1977.
955. RAO, M. L., RAO, G. S., HOLLER, M., BRUER, H., SCHATTENBERG, P. J., AND STEIN, W. D.: Uptake of cortisol by isolated rat liver cells. A phenomenon indicative of carrier-mediation and simple diffusion. Hoppe-Seylers Z. Physiol. Chem. **357:** 573–584, 1976.
956. RAPPAPORT, A. M.: Physioanatomical basis of toxic liver injury. *In* Toxic Injury of the Liver, ed. by E. Farber and M. M. Fisher, pp. 1–57, Marcel Dekker, New York, 1979.
957. RAPPAPORT, A. M.: Hepatic blood flow: Morphologic aspects and physiologic regulation. Int. Rev. Physiol. **21:** 1–63, 1980.
958. RASSERO, J. A., AND RODRIQUEZ-GARAY, E. A.: The measurement of bile acid-dependent and independent fraction of rat bile. Acta Physiol. Lat. Am. **28:** 309–313, 1978.
959. RATZAN, K. R., BAKER, H. B., AND LAUREDO, I.: Excretion of cefamandole, cefazolin, and cephalothin into T-tube bile. Antimicrob. Agents Chemother. **13:** 985–987, 1978.
960. REAVEN, E. P., AND REAVEN, G. M.: Evidence that microtubules play a permissive role in hepatocyte very low density lipoprotein secretion. J. Cell Biol. **84:** 28–39, 1980.
961. REDINGER, R. N., AND SMALL, D. M.: Bile composition, bile salt metabolism and gallstones. Arch. Intern. Med. **130:** 618–630, 1972.
962. REDINGER, R. N., AND SMALL, D. M.: Primate biliary physiology. VIII. The effect of phenobarbital upon bile salt synthesis and pool size, biliary lipid secretion, and bile composition. J. Clin. Invest. **52:** 161–172, 1973.
963. REFSVIK, T.: Excretion of methyl mercury in rat bile: The effect of diethylmaleate, cyclohexene oxide and acrylamide. Acta Pharmacol. Toxicol. **42:** 135–141, 1978.
964. REICHEN, J., AND BERK, P. D.: Isolation of an organic anion binding protein from rat liver plasma membrane fractions by affinity chromatography. Biochem. Biophys. Res. Commun. **91:** 494–489, 1979.
965. REICHEN, J., BERMAN, M. D., AND BERK, P. D.: The role of microfilaments and of microtubules in taurocholate uptake by isolated rat liver cells. Biochim. Biophys. Acta **643:** 126–133, 1981.
966. REICHEN, J., BLITZER, B., AND BERK, P. D.: Binding of unconjugated and conjugated sulfobromophthalein to rat liver plasma membrane fractions in vitro. Biochim. Biophys. Acta **640:** 298–312, 1981.
967. REICHEN, J., AND PAUMGARTNER, G.: Uptake of bile acids by perfused rat liver. Am. J. Physiol. **231:** 734–742, 1976.
968. REICHEN, J., AND PAUMGARTNER, G.: Relationship between bile flow and Na^+,K^+-adenosinetriphosphatase in liver plasma membranes enriched in bile canaliculi. J. Clin. Invest. **60:** 429–434, 1977.
969. REICHEN, J., AND PAUMGARTNER, G.: Inhibition of hepatic Na^+, K^+-adenosinetriphosphatase in taurolithocholate-induced cholestasis in the rat. Experientia (Basel) **35:** 1186–1188, 1979.
970. REICHEN, J., AND PAUMGARTNER, G.: Excretory function of the liver. Int. Rev. Physiol. **21:** 103–150, 1980.
971. REICHEN, J., PREISIG, R., AND PAUMGARTNER, G.: Influence of chemcial structure on hepatocellular uptake of bile acids. *In* Bile Acid Metabolism in Health and Disease, ed. by G. Paumgartner and A. Stiehl, pp. 113–123, MPT Press, Lancaster, 1976.
972. REICHEN, J., AND SIMON, F. R.: Cholestasis. *In* The Liver, Biology and Pathobiology, ed. by I. M. Arias, H. Popper, D. Schachter, and D. A. Shafritz, pp. 785–800, Raven Press, New York, 1982.
973. REINKE, L. A., BELINSKY, S. A., EVANS, R. K., KAUFFMAN, F. C., AND THURMAN, R. G.: Conjugation of *p*-nitrophenol in the perfused rat liver: The effect of substrate concentration and carbohydrate reserves. J. Pharmacol. Exp. Ther. **217:** 863–870, 1981.
974. REINKE, L. A., KAUFFMAN, F. C., EVANS, R. K., BELINSKY, S. A., AND THURMAN, R. G.: *p*-Nitrophenol conjugation in perfused liver from normal and phenobarbital-treated rats: Influence of nutritional state. Res. Commun. Chem. Path. Pharmacol. **23:** 185–193, 1979.
975. REMMEL, R. P., POHL, L. R., AND ELMER, G. W.: Influence of the intestinal mciroflora on the elimination of warfarin in the rat. Drug Metab. Dispos. **9:** 410–414, 1981.
976. RENAUD, G., FOLIOT, A., AND INFANTE, R.: Increased uptake of fatty acids by the isolated rat liver after raising the fatty acid binding protein concentration with clofibrate. Biochem. Biophys. Res. Commun. **80:** 327–334, 1978.
977. RENSTON, R. H., JONES, A. L., CHRISTIANSEN, W. D., HRADEK, G. T., AND UNDERDOWN, B. J.: Evidence for a vesicular transport mechanism in hepatocytes for biliary secretion of immunoglobulin A. Science **208:** 1276–1278, 1980.
978. RENSTON, R. H., MALONEY, D. G., JONES, A. L., HRADEK, G. T., WONG, K. Y., AND GOLDFINE, I. D.: Bile secretory apparatus: Evidence for a vesicular transport mechanism for proteins in the rat, using horseradish peroxidase and [^{125}I]-insulin. Gastroenterology **78:** 1373–1388, 1980.
979. REYES, H.: The enigma of intrahepatic cholestasis of pregnancy: Lessons from Chile. Hepatology **2:** 87–96, 1982.
980. REYES, H., AND KERN, F.: Effect of pregnancy on bile flow and biliary lipids in the hamster. Gastroenterology **76:** 144–150, 1979.
981. REYES, H., LEVI, A. J., GATMAITAN, Z., AND ARIAS, I. M.: Studies of Y and Z, two hepatic cytoplasmic organic anion-binding proteins: Effect of drugs, chemicals, hormones and cholestasis. J. Clin. Invest. **50:** 2242–2252, 1971.
982. REYES, H., RIBALTA, J., GONZALEZ, M. C., SEGOVIA, N., AND OBERHAUSER, E.: Sulfobromophthalein clearance tests before and after ethinyl estradiol administration, in women and men with familial history of intrahepatic cholestasis of pregnancy. Gastroenterology **81:** 226–231, 1981.
983. REYNOLDS, J., GYURE, L., ANDREW, E., AND HALL, J. G.: Studies of the transport of polyclonal IgA antibody from blood to bile in rats. Immunology **39:** 463–467, 1980.
984. RICCI, G. L., AND FEVERY, J.: Cholestatic action of somatostatin in the rat: effect on the different fractions of bile secretion. Gastroenterology **81:** 552–562, 1981.
985. RICHARDS, M., AND COUSINS, R.: Mammalian zinc homeostasis: Requirement for RNA and metallothionein synthesis. Biochem. Biophys. Res. Commun. **64:** 1215–1223, 1975.
986. RICHARDS, M., AND COUSINS, R.: Influence of parenteral zinc and actinomycin D on tissue zinc uptake and the synthesis of a zinc-binding protein. Bioinorg. Chem. **4:** 215–224, 1975.
987. RIGGS, C. E., BENJAMIN, R. S., SERPICK, A. A., AND BACHUR, N. R.: Biliary dispoeition of adriamycin. Clin. Pharmacol. Ther. **22:** 234–241, 1977.
988. RITSCHEL, W. A., BRADY, M. E., AND TAN, H. S. I.: First pass effect of coumarin in man. Int. J. Clin. Pharmacol. Biopharm. **17:** 99–103, 1979.
989. RITT, D. J., AND COMBES, B.: Enhancement of apparent excretory maximum of sulphobromophthalein sodium (BSP) by taurocholate and dehydrocholate. J. Clin. Invest. **46:** 1106–1109, 1967.
990. ROBERTS, R. J., KLAASSEN, C. D., AND PLAA, G. L.: Maximum biliary excretion of bilirubin and sulfobromophthalein during anesthesia-induced alteration of rectal temperature. Proc. Soc. Exp. Biol. Med. **125:** 313–316, 1967.
991. ROBERTS, R. J., AND PLAA, G. L.: Alteration of the plasma disappearance and biliary excretion patterns of exogenously administered bilirubin by α-naphthylisothiocyanate. J. Pharmacol. Exp. Ther. **155:** 330–336, 1967.
992. ROBERTS, R. J., AND PLAA, G. L.: Effect of phenobarbital on the excretion of exogenous bilirubin load. Biochem. Pharmacol. **16:** 827–835, 1967.
993. ROBERTS, R. J., AND PLAA, G. L.: Alteration in biliary bilirubin content and non-erythropoietically derived bilirubin synthesis in rats after α-naphthylisothiocyanate administration. J. Pharmacol. Exp. Ther. **161:** 382–388, 1968.
994. ROBINSON, J. D., AND FLASHNER, M. S.: The (Na^+ + K^+)-activated ATPase enzymatic and transport properties. Biochim. Biophys. Acta **549:** 145–176, 1979.
995. RODGERS, R. M., TAYLOR, S. M., DICKINSON, R. G., ILIAS, A. M., LYNN, R. K., AND GERBER, N.: Metabolism and choleretic effect of naltrexone in the isolated perfused rat liver. Drug Metab. Dispos. **8:** 390–396, 1980.
996. ROERIG, D. L., HASEGAWA, A. T., AND WANG, R. I. H.: Role of enteroheptic circulation in the analgesic action of 1-α-acetylmethadol in the rat. Drug Metab. Dispos. **7:** 306–309, 1979.
997. ROERIG, D. L., HASEGAWA, A. T., AND WANG, R. I. H.: Enteroheptic circulation of 1-α-acetylmethadol in the rat. J. Pharmacol. Exp. Ther. **213:** 284–288, 1980.
998. ROHR, G., KERN, H., AND SCHEELE, G.: Enteropancreatic circulation of digestive enzymes does not exist in the rat. Nature (Lond.) **292:** 470–472, 1981.
999. ROLLINS, D. E., AND KLAASSEN, C. D.: Biliary excretion of drugs in man. Clin. Pharmacokin. **4:** 368–379, 1979.
1000. ROS, E., SMALL, D. M., AND CAREY, M. C.: Effects of chlorpromazine hydrochloride on bile salt synthesis, bile formation and biliary lipid secretion in the rhesus monkey: A model for chlorpromazine-induced cholestasis. Eur. J. Clin. Invest. **9:** 29–41, 1979.

1001. ROSENBLUM, J. L., AND ALPERS, D. H.: Hepatic and pancreatic uptake of pancreatic amylase in the rabbit. Gastroenterology **80:** 1264, 1981.
1002. ROSENTHAL, S. M., AND WHITE, E. C.: Clinical application of the bromsulphthalein test for hepatic function. J.A.M.A. **84:** 1112–1114, 1925.
1003. ROSS, B. D.: Perfusion Techniques in Biochemistry: A laboratory Manual. Clarendon Press, Oxford, 1972.
1004. ROUTLEDGE, P. A., AND SHAND, D. G.: Clinical pharmacokinetics of propranolol. Clin. Pharmacokin. **4:** 73–90, 1979.
1005. ROZMAN, K., ROZMAN, T., BALLHORN, L., AND GREIM, H.: Hexadecane enhances non-biliary, intestinal excretion of stored hexachlorobenzene by rats. Toxicology **24:** 107–113, 1982.
1006. ROZMAN, K., ROZMAN, T., AND GREIM, H.: Enhanced fecal elimination of stored hexachlorobenzene from rats and rhesus monkeys by hexadecane or mineral oil. Toxicology **22:** 33–44, 1981.
1007. ROZMAN, K., ROZMAN, T., GREIM, H., NIEMAN, I. J., AND SMITH, G. S.: Use of aliphatic hydrocarbons in feed to decrease body burdens of lipophilic toxicants in livestock. J. Agric. Food Chem. **30:** 98–100, 1982.
1008. ROZMAN, K. K., ROZMAN, T. A., WILLIAMS, J., AND GREIM, H. A.: Effect of mineral oil and/or cholestyramine in the diet on biliary and intestinal elimination of 2,4,5,2′,4′,5′-hexabromobiphenyl in rhesus monkey. J. Toxicol. Environ. Health **9:** 611–618, 1982.
1009. ROZMAN, T., BALLHORN, L., ROZMAN, K., KLAASSEN, C., AND GREIM, H.: Effect of cholestyramine on the disposition of pentachlorophenol in rhesus monkeys. J. Toxicol. Environ. Health **10:** 277–283, 1982.
1010. ROZMAN, T., ROZMAN, K., WILLIAMS, J., AND GREIM, H.: Enhanced fecal excretion of mirex in rhesus monkeys by 5% mineral oil in the diet. Drug Chem. Toxicol. **4:** 251–262, 1981.
1011. RUBIN, P., YEE, Y.-G., ANDERSON, M., AND BLASCHKE, T.: Prazosin first-pass metabolism and hepatic extraction in the dog. J. Cardiovasc. Pharmacol. **1:** 641–647, 1979.
1012. RUDDICK, J. A., CRAIG, J., STAVRIK, B., WILLES, R. F., AND COLLINS, B.: Uptake, distribution and metabolism of [^{14}C]amaranth in the female rat. Food Cosmet. Toxicol. **17:** 435–442, 1979.
1013. RUDMAN, D., AND KENDALL, F. E.: Bile acid content of human serum. II. The binding of cholanic acids by human plasma protein. J. Clin. Invest. **36:** 538–542, 1957.
1014. RUIFROK, P. G., AND MEIJER, D. K. F.: Sodium ion-coupled uptake of taurocholate by rat-liver plasma membrane vesicles. Liver **2:** 28–34, 1982.
1015. RUSSELL, I. S., FLECK, A., AND BURNETT, W.: The protein content of human bile. Clin. Chim. Acta **10:** 210–213, 1964.
1016. RUSSELL, J. Q., AND KLAASSEN, C. D.; Species variation in the biliary excretion of ouabain. J. Pharmacol. Exp. Ther. **183:** 513–519, 1972.
1017. RUSSELL, J. Q., AND KLAASSEN, C. D.: Biliary excretion of cardiac glycosides. J. Pharmacol. Exp. Ther. **186:** 455–462, 1973.
1018. RYAN, A. J., AND WRIGHT, S. E.: The excretion of some azo dyes in rat bile. J. Pharm. Pharmacol. **13:** 492–495, 1961.
1019. SALASPURO, M. P., PIKKARAINEN, P., SIPPONEN, P., VUORI, E., AND MIETTINEN, T. A.: Hepatic copper in primary biliary cirrhosis: Biliary excretion and response to penicillamine treatment. Gut **22:** 901–906, 1981.
1020. SALEN, G., CALALILLO, A., VERGA, D., BAGAN, E., TINT, G. S., AND SHEFER, S.: Effect of high and low doses of ursodeoxycholic acid on gallstone dissolution in humans. Gastroenterology **78:** 1412–1418, 1980.
1021. SALHAB, A. S., AND DUJOVNE, C. A.: Chlorpromazine uptake by isolated rat hepatocytes. Proc. Soc. Exp. Biol. Med. **161:** 270–274, 1979.
1022. SAMA, C., LARUSSO, N. F., LOPEZ DEL PINO, V., AND THISTLE, J. L.: Effects of acute bile acid administration on biliary lipid secretion in healthy volunteers. Gastroenterology **82:** 515–525, 1982.
1023. SAMUELS, A. M., AND CAREY, M. C.: Effects of chlorpromazine hydrochloride and its metabolites on Mg^{2+}- and Na^+,K^+-ATPase activities of canalicular-enriched rat liver plasma membranes. Gastroenterology **74:** 1183–1190, 1978.
1024. SAMUELSON, K., ALY, A., JOHANSSON, C., AND NORMAN, A.: Serum and urinary bile acids in patients with primary biliary cirrhosis. Scand. J. Gastroenterol. **17:** 121–128, 1982.
1025. SATTLER, V. R. W., SCHMIEDEBERG, W., AND SEILER, K. U.: Possible influence on the enterohepatic digitoxin circulation in humans. Arzneim.-Forsch. **27:** 1615–1617, 1977.
1026. SCRATCHERD, T.: Electrolyte composition and control of biliary secretion in the cat and rabbit. *In* The Biliary System, ed. by W. Taylor, pp. 515–528, F. A. Davis, Philadelphia, 1965.
1027. SCHAFER, E. A.: Textbook of Physiology, vol. 1, ed. by J. Young, p. 444, Pentland, Edinburgh and London, 1898.
1028. SCHAFFNER, F., AND POPPER, H.: Causation and consequences of cholestasis: an overview. *In* Jaundice, ed. by C. A. Goresky, and M. M. Fisher, pp. 329–349, Plenum Press, New York, 1975.
1029. SCHANKER, L. S.: Secretion of organic compounds in bile. *In* Handbook of Physiology, Section 6: Alimentary Canal, vol. V, ed. by C. F. Code, and W. Heidel, pp. 2433–2449, American Physiological Society, Washington, DC, 1968.
1030. SCHANKER, L. S., AND HOGBEN, C. A. M.: Biliary excretion of inulin, sucrose, and mannitol: Analysis of bile formation. Am. J. Physiol. **200:** 1087–1090, 1961.
1031. SCHANKER, L. S., AND SOLOMON, H. M.: Active transport of quaternary ammonium compounds into bile. Am. J. Physiol. **204:** 829–832, 1963.
1032. SCHANNE, F. A. X., PFAU, R. G., AND FARBER, J. L.: Galactosamine-induced cell death in primary cultures of rat hepatocytes. Am. J. Pathol. **100:** 25–38, 1980.
1033. SCHARSCHMIDT, B. F., AND KEEFFE, E. B.: Isolation of a rat liver plasma membrane fraction of probable canalicular origin preparative technique, enzymatic profile, composition, and solute transport. Biochim. Biophys. Acta. **646:** 369–381, 1981.
1034. SCHARSCHMIDT, B. F., KEEFFE, E. B., VESSEY, D. A., BLANKENSHIP, N. M., AND OCKNER, R. K.: In vitro effect of bile salts on rat liver plasma membrane, lipid fluidity, and ATPase activity. Hepatology **1:** 137–145, 1981.
1035. SCHARSCHMIDT, B. F., AND SCHMID, R.: The micellar sink. A quantitative assessment of the association of organic anions with mixed micelles and other macromolecular aggregates in rat bile. J. Clin. Invest. **62:** 1122–1131, 1978.
1036. SCHARSCHMIDT, B. F., AND STEPHENS, J. E.: Transport of sodium, chloride and taurocholate by cultured rat hepatocytes. Proc. Natl. Acad. Sci. U.S.A. **78:** 986–990, 1981.
1037. SCHARSCHMIDT, B. F., VAN DYKE, R. W., AND STEPHENS, J. E.: Chloride transport by intact rat liver and cultured rat hepatocytes. Am. J. Physiol. **242:** G628–G633, 1982.
1038. SCHARSCHMIDT, B. F., WAGGONER, J. G., AND BERK, P. D.: Hepatic organic anion uptake in the rat. J. Clin. Invest. **56:** 1280–1292, 1975.
1040. SCHERSTEN, T., NILSSON, S., CAHLIN, E., FILIPSON, M., AND BRODIN-PERSSON, G.: Relationship between the biliary excretion of bile acids and the excretion of water, lecithin, and cholesterol in man. Eur. J. Clin. Invest. **1:** 242–247, 1971.
1041. SCHMID, R.: Bilirubin metabolism: State of the art. Gastroenterology **74:** 1307–1312, 1980.
1042. SCHMOLDT, A., BENTHE, H. F., AND HABERLAND, G.: Impaired biliary excretion of digitoxin and its metabolites after treatment with polychlorinated biphenyls. Toxicol. Appl. Pharmacol. **47:** 483–491, 1979.
1043. SCHULZE, P.-J., AND CZOK, G.: Studies on the decrease in the bile flow produced by sulfobromophthalein. Toxicol. Appl. Pharmacol. **28:** 406–417, 1974.
1044. SCHULZE, P.-J., AND CZOK, G.: Reduced bile flow in rats during sulfobromophthalein infusion. Toxicol. Appl. Pharmacol. **32:** 213–224, 1975.
1045. SCHULTZE, P.-J., CZOK, G., AND KELLER, E.: The effects of pretreatment with phenobarbital (PB) and sulfobromophthalein (BSP) on the metabolism and the biliary excretion of BSP in the rat. Arzneim.-Forsch. **29:** 1521–1528, 1979.
1046. SCHULZE, I., STROVER, F., AND ULLRICH, K. J.; Lipid soluble weak organic acid buffers as "substrate" for pancreatic secretion. Plfuegers Arch. **323:** 121–140, 1971.
1047. SCHWARTZ, A. L., RUP, D., AND LODISH, H. F.: Difficulties in the quantification of asialoglycoprotein receptors on the rat hepatocyte. J. Biol. Chem. **255:** 9033–9036, 1980.
1048. SCHWARTZ, C. C., BERMAN, M., VLAHCEVIC, Z. R., HALLORAN, L. G., GREGORY, D. H., AND SWELL, L.: Multicompartmental analysis of cholesterol metabolism in man. Characterization of the hepatic bile acid and biliary cholesterol precursor sites. J. Clin. Invest. **61:** 408–423, 1978.
1049. SCHWARZ, F. J., AND MATRONE, G.: Methodological studies on the uptake of zinc by 3T3 cells. Proc. Soc. Exp. Biol. Med. **149:** 888–892, 1975.
1050. SCHWARZ, L. R., AND BARTH, C. A.: Taurocholate uptake by adult rat hepatocytes in primary culture. Hoppe-Seyler's Z. Physiol. Chem. **360:** 1117–1120, 1979.
1051. SCHWARZ, L. R., BURR, R., SCHWENK, M., PFAFF, E., AND GREIM, H.: Uptake of taurocholic acid into isolated rat-liver cells. Eur. J. Biochem. **55:** 617–623, 1975.
1052. SCHWARZ, L. R., GOTZ, R., AND KLAASSEN, C. D.: Uptake of sulfobromophthalein-glutathione conjugate by isolated hepatocytes. Am. J. Physiol. **239:** C118–C123, 1980.
1053. SCHWARZ, L. R., AND GREIM, H.: Isolated hepatocytes: An analytical tool in hepatotoxicology. *In* Frontiers in Liver Disease, ed. by P. D. Berk and T. C. Chalmers, Neuherberg, W. Germany, 1981.
1054. SCHWARZ, L. R., SCHWENK, M., AND GREIM, H.: Review: Current concepts in intrahepatic cholestasis. Acta Hepato-Gastroenterol. **24;** 210–215, 1977.
1055. SCHWARZ, L. R., SCHWENK, M., PFAFF, E., AND GREIM, H.: Cholestatic steroid hormones inhibit taurocholate uptake into isolated rat hepatocyte. Biochem. Pharmacol. **26:** 2433–2437, 1977.
1056. SCHWARZ, L. R., SUMMER, K.-H., AND SCHWENK, M.: Transport and metabolism of bromosulfophthalein by isolated rat liver cells. Eur. J. Biochem. **94:** 617–622, 1979.
1057. SCHWENK, M.: Transport system of isolated hepatocytes. Arch. Toxicol. **44:** 113–126, 1980.
1058. SCHWENK, M., BURR, R., AND PFAFF, E.: Influence of viability on bromosulfophthalein uptake by isolated hepatocytes. Naunyn-Schmiedeberg's Arch. Pharmacol. **295:** 99–102, 1976.
1059. SCHWENK, M., BURR, R., SCHWARZ, L., AND PFAFF, E.: Uptake of bromosulfophthalein by isolated liver cells. Eur. J. Biochem. **64:** 189–197, 1976.

1060. SCHWENK, M., AND LOPEZ DEL PINO, V.: Uptake of estrone sulfate by isolated rat liver cells. J. Steroid Biochem. **13:** 669–673, 1980.
1061. SCHWENK, M., WIEDMANN, T., AND REMMER, H.: Uptake, accumulation and release of ouabain by isolated rat hepatocytes. Naunyn-Schmiedeberg's Arch. Pharmacol. **316:** 340–344, 1981.
1062. SEEFELD, M. D., ALBRECHT, R. M., GILCHRIST, K. W., AND PETERSON, R. E.: Blood clearance tests for detecting 2,3,7,8-tetrachlordibenzo-*p*-dioxin hepatotoxicity in rats and rabbits. Arch. Environ. Contam. Toxicol. **9:** 317–327, 1980.
1063. SEEFELD, M. D., ALBRECHT, R. M., AND PETERSON, R. E.: Effects of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin on indocyanine green blood clearance in rhesus monkeys. Toxicology **14:** 263–272, 1979.
1064. SELLMAN, R., KANTO, J., AND PEKKARINEN, J.: Biliary excretion of diazepam and its metabolites in man. Acta Pharmacol. Toxicol. **37:** 242–249, 1975.
1065. SEYLE, H., AND MECS, I.: Effect upon drug toxicity of surgical interference with hepatic or renal function. Parts 1 and 2. Acta Hepato-Gastroenterol. **21:** 191–202, 266–273, 1974.
1066. SEWELL, R. B., HARDY, K. J., SMALLWOOD, R. A., AND HOFFMAN, N. E.: The hepatic transport of sodium (^{14}C)taurocholate in foetal sheep. Clin. Exp. Pharmacol. Physiol. **6:** 117–120, 1979.
1067. SEWELL, R. B., HOFFMAN, N. E., SMALLWOOD, R. A., AND COCKBAIN, S.: Bile acid structure and bile formation: A comparison of hydroxy and keto bile acids. Am. J. Physiol. **238:** 10–17, 1980.
1068. SHACKMAN, R., GRABER, I. G., AND MELROSE, D. G.: Liver blood flow and general anesthesia. Clin. Sci. **12:** 307–315, 1953.
1069. SHADER, R. I., GREENBLATT, D. J., HARMATZ, J. S., FRANKE, K., AND KOCH-WESER, J.: Absorption and disposition of chlordiazepoxide in young and elderly male volunteers. J. Clin. Pharmacol. **17:** 709–718, 1977.
1070. SHAFFER, E., AND PRESHAW, R.: Effects of sulfobromophthalein excretion on biliary lipid secretion in humans and dogs. Am. J. Physiol. **240:** 85–89, 1981.
1071. SHAFFER, E. A., AND SMALL, D. M.: Biliary lipid secretion in cholesterol gallstone disease. The effect of cholecystectomy and obesity. J. Clin. Invest. **59:** 828–840, 1977.
1072. SHAIKH, Z. A., AND SMITH, J. C.: The biosynthesis of metallothionein in rat liver and kidney after administration of cadmium. Chem.-Biol. Interactions **15:** 327–336, 1976.
1073. SHAND, D. G., EVANS, G. H., AND NIES, A. S.: The almost complete hepatic extraction of propranolol during inravenous administration in the dog. Life Sci. **10:** 1417–1421, 1971.
1074. SHAND, D. G., KORNHAUSER, D. M., AND WILKINSON, G. R.: Effects of route of administration and blood flow on hepatic drug elimination. J. Pharmacol. Exp. Ther. **195:** 424–432, 1975.
1075. SHAND, D. G., AND RANGNO, R. E.: The disposition of propranolol. I. Elimination during oral absorption in man. Pharmacology **7:** 159–168, 1972.
1076. SHAND, D., G., RANGNO, R. E., AND EVANS, G. H.: The disposition of propranolol. II. Hepatic elimination in the rat. Pharmacology **8:** 344–352, 1972.
1077. SHARMA, J. N., AND PRASAD, C. R.: Effect of chlorpromazine on the bile secretion in dogs. Indian J. Med. Res. **55:** 258–260, 1967.
1078. SHAW, H. M., CAPLE, I., AND HEATH, T.: Effect of ethacrynic acid on bile formation in sheep, dogs, rats, guinea pigs and rabbits. J. Pharmacol. Exp. Ther. **182:** 27–33, 1972.
1079. SHAW, H. M., AND HEATH, T. J.: Regulation of bile formation in rabbits and guinea pigs. Q. J. Exp. Physiol. **59:** 93–102, 1974.
1080. SHAW, H. M., AND HEATH, T. J.: Bile salts and bile formation in rats, rabbits, and guinea pigs. Comp. Biochem. Physiol. **50A:** 615–619, 1975.
1081. SHEFER, S., SALEN, G., HAUSER, S., DAYAL, B., AND BATTA, A. K.: Metabolism of iso-bile acids in the rat. J. Biol. Chem. **257:** 1401–1406, 1982.
1082. SHELINE, G. E., CHAIKOFF, I. L., JONES, H. B., AND MONTGOMERY, M. L.: Studies on the metabolism of zinc with the aid of its radioactive isotope. I. The excretion of administered zinc in urine and feces. J. Biol. Chem. **147:** 409–414, 1943.
1083. SHERRILL, B. C., INNERARITY, T. L., AND MAHLEY, R. W.: Rapid hepatic clearance of the canine lipoproteins containing only the E apoprotein by a high affinity receptor. Identity with the chylomicron remnant transport process. J. Biol. Chem. **255:** 1804–1807, 1980.
1084. SHOEMAKER, D., GORMLEY, P., AND CYSYK, R.: Biliary excretion f 4'-(9-acrindinylamino)methanesulfon-m-anisidide (AMSA) in rats: Effects of pretreatment with diethyl maleate, phenobarbital, and metyrapone. Drug Metab. Dispos. **8:** 467–468, 1980.
1085. SHORT, C. R., KINDEN, D. A., AND STITH, R.: Fetal and neonatal development of the microsomal monooxygenase system. Drug Metab. Rev. **5:** 1–42, 1976.
1086. SHORT, J., ARMSTRONG, N. B., GAZA, D. J., AND LIEBERMAN, I.: Hormones and amino acids and the control of nuclear DNA replication in liver. *In* Liver Regeneration After experimental Injury, ed. by R. Lesh and W. Reutter, pp. 296–309, Stratton Medical Book Corp., New York, 1973.
1087. SIDDIK, Z. H., DREW, R., AND GRAM, T. E.: Metabolism and biliary excretion of sulfobromophthalein in vitamin A deficiency. Biochem. Pharmacol. **29:** 2583–2588, 1980.
1088. SIEGERS, C. P., AND SCHUTT, A.: Dose-dependent biliary and renal excretion of paracetamol in the rat. Pharmacology **18:** 175–179, 1979.
1089. SIMMONS, F., ROSS, A. P. J., AND BOUCHIER, I. A. D.: Alterations in hepatic bile composition after cholecystectomy. Gastroenterology **63:** 466–471, 1972.
1090. SIMON, F. R., GONZALEZ, M., SUTHERLAND, E., ACCATINO, L., AND DAVIS, R. A.: Reversal of ethinyl estradiol-induced bile secretory failure with Triton WR-1339. J. Clin. Invest. **65:** 851–860, 1980.
1091. SIMON, F. R., SUTHERLAND, E., AND ACCATINO, L.: Stimulation of hepatic sodium and potassium-activated adenosine triphosphatase activity by phenobarbital. Its possible role in regulation of bile flow. J. Clin. Invest. **59:** 849–861, 1977.
1092. SIMON, F. R., SUTHERLAND, E. M., AND GONZALEZ, M.: Regulation of bile salt transport in rat liver: Evidence that increased maximum bile salt secretory capacity is due to increased cholic acid receptors. J. Clin. Invest. **70:** 401–411, 1982.
1093. SIMONS, P. C., AND JAGT, D. L. V.: Bilirubin binding to human liver ligandin (glutathione S-transferase). J. Biol. Chem. **255:** 4740–4744, 1980.
1094. SKAARE, J. U.: Studies on the biliary excretion and metabolites of the antioxidant ethoxyquin, 6-ethoxy-2,2,4-trimethyl-1,2-dihydroquinoline in the rat. Xenobiotica **9:** 659–668, 1979.
1095. SKELTON, F. S., WITSCHI, H., AND PLAA, G. L.: The effects of cycloheximide, actinomycin D and ethionine on the biliary excretion of labelled alpha-naphthylisothiocyanate in rats. Exp. Mol. Pathol. **23:** 171–180, 1975.
1096. SKILLETER, D. N., AND CAIN, K.: Effects of thiol agents on the accumulation of cadmium by rat liver parenchymal and Kupffer cells. Chem.-Biol. Interact. **37:** 289–298, 1981.
1097. SMALL, D. M.: Physico-chemical studies of cholesterol gallstone formation. Gastroenterology **52:** 607–610, 1967.
1098. SMALL, D. M.: The physical chemistry of cholanic acids. *In* The Bile Acids: Chemistry, Physiology and Metabolism, vol. 1, ed. by P. P. Nair and D. Kritchevsky, pp. 249–356. Plenum Press, New York, 1971.
1099. SMALL, D. M., AND ADMIRAND, W.: Solubility of bile salts. Nature (Lond.) **221:** 265–267, 1969.
1100. SMALL, D. M., BOURGES, M., AND DERVICHIAN, D. G.: Ternary and quaternary aqueous systems containing bile salt, lecithin and cholesterol. Nature (Lond.) **211:** 816–818, 1966.
1101. SMALL, D. M., DOWLING, R. H., AND REDINGER, R. N.: The enteroheptic circulation of bile salts. Arch. Intern. Med. **130:** 552–573, 1972.
1102. SMALL, D. M., AND RAPO, S.: Source of abnormal bile in patients with cholesterol gallstones. N. Engl. J. Med. **283:** 53–57, 1970.
1103. SMALLWOOD, R. A., AND HOFFMAN, N. E.: Bile acid structure and biliary secretion of cholesterol and phospholipid in the cat. Gastroenterology **71:** 1064–1066, 1976.
1104. SMITH, D. S., AND FUJIMOTO, J. M.: Alterations produced by novobiocin during biliary excretion of morphine, morphine-3-glucuronide and other compounds. J. Pharmacol. Exp. Ther. **188:** 504–515, 1974.
1105. SMITH, N. D., AND BOYER, J. L.: Permeability characteristics of the bile duct in the rat. Am. J. Physiol. **242:** G52–G57, 1982.
1106. SMITH, R. L.: The biliary excretion and enterohepatic circulation of drugs and other organic compounds. Prog. Drug Res. **9:** 299–360, 1966.
1107. SMITH, R. L.: The Excretory Function of Bile: The Elimination of Drugs and Toxic Substances in Bile, Chapman and Hall, London, 1973.
1108. SOBOCINSKI, P. Z., CANTERBURY, W. J., JR., MAPES, C. A., AND DINTERMAN, R. E.: Involvement of hepatic metallotioneins in hypozincemia associated with bacterial infection. Am. J. Physiol. **234:** E399–E406, 1978.
1109. SOLOWAY, R. D., HOFMANN, A. F., THOMAS, P. J., SCHOENFIELD, L. J., AND KLEIN, P. D.: Triketocholanoic (dehydrocholic) acid. Hepatic metabolism and effect on bile flow and biliary lipid secretion in man. J. Clin. Invest. **52:** 715–724, 1973.
1110. SOLYMOSS, B., AND ZSIGMOND, G.: Effect of various steroids on the hepatic glucuronidation and biliary excretion if bilirubin. Can. J. Physiol. Pharmacol. **51:** 319–323, 1973.
1111. SOMANI, S. M., BAJAJ, R. A., CALVEY, T. N., AND NORMAN, T.:Effect of phenobarbitone on the elimination of neostigmine and its metabolites in bile. Biochem. Pharmacol. **29:** 2256–2257, 1980.
1112. SONG, C. S., BERANBAUM, E. R., AND ROTHSCHILDT, M. A.: The role of serum albumin in hepatic excretion of iodipamide. Invest. Radiol. **11:** 39–44, 1976.
1113. SPELLMAN, S. J., SHAFFER, E. A., AND ROSENTHALL, L.: Gallbladder emptying in response to cholecystokinin. A cholescintigraphic study. Gastroenterology **77:** 115–120, 1979.
1114. SPERBER, I.: Secretion of organic anions in the formation of urine and bile. Pharmacol. Rev. **11:** 109–134, 1959.
1115. Sperber, I.: Biliary excretion and choleresis. *In* Proceedings of the First International Pharmacology Meeting, vol. 4, pp. 137–143, Pergamon, Oxford, 1963.
1116. SPERBER, I.: Biliary secretion of organic anions and its influence on bile flow. *In* The Biliary System, ed. by W. Taylor, pp. 457–467, F. A. Davis, Philadelphia, 1965.
1117. SQUIBB, K. S., COUSINS, R. J., AND FELDMAN, S. L.: Control of zinc-thionein synthesis in rat liver. Biochem. J. **164:** 223–228, 1977.

1118. STACEY, N. H., AND KLAASSEN, C. D.: Uptake of ouabain by isolated hepatocytes from livers of developing rats. J. Pharmacol. Exp. Ther. **211:** 360–363, 1979.
1119. STACEY, N. H., AND KLAASEN, C. D.: Cadmium uptake by isolated rat hepatocytes. Toxicol. Appl. Pharmacol. **55:** 448–455, 1980.
1120. STACEY, N. H., AND KLAASSEN, C. D.: Uptake of galactose, ouabain and taurocholate into centrilobular and periportal enriched hepatocyte subpopulations. J. Pharmacol. Exp. Ther, **216:** 634–639, 1981.
1121. STACEYU, N. H., AND KLAASSEN, C. D.: Zinc uptake by isolated rat hepatocytes. Biochim. Biophys. Acta **640:** 693–697, 1981.
1122. STAND, F., ROSOFF, B., WILLIAMS, G. L., AND SPENCER, H.: Tissue distribution studies of ionic and chelated Zn^{65} in mice. J. Pharmacol. Exp. Ther. **138:** 399–404, 1962.
1123. STASIEWICZ, J., AND WORMSLEY, K. G.: Functional control of the biliary tract. Acta Hepato-Gastroenterol. **21:** 450–468, 1974.
1124. STEER, C. J., AND ASHWELL, G.; Studies on a mammalian hepatic binding protein specific for asialoglycoprotein: Evidence for receptor recycling in isolated rat hepatocytes. J. Biol. Chem. **255:** 3008–3013, 1980.
1125. STEER, C. J., KEMPNER, E. S., AND ASHWELL, G.: Molecular size of the hepatic receptor for asialoglycoproteins determined in situ by radiation inactivation. J. Biol. Chem. **256:** 5851–5856, 1981.
1126. STEFKO, P. L., AND ZBINDEN, G.: Effect of chlorpromazine, chlordiazepoxide, diazepam and chlorprothixene on bile flow and intrabiliary pressure in cholecystectomized dogs. Am. J. Gastroenterol. **39:** 410–417, 1963.
1127. STEGE, T. E., LOOSE, L. D., AND DILUZIO, N. R.: Comparative uptake of sulfobromophthalein by isolated kupffer and parenchymal cells. Proc. Soc. Exp. Biol. Med. **149:** 455–461, 1975.
1128. STEGMANN, R., AND BICKEL, M. H.: Dominant role for tissue binding in the first-pass extraction of imipramine by the perfused rat liver. Xenobiotica **7:** 737–746, 1977.
1129. STEIN, L. B., MISHKIN, S., FLEISCHNER, G., GATMAITAN, Z., AND ARIAS, I. M.: Effect of fasting on hepatic ligandin, Z protein, and organic anion transfer from plasma in rats. Am. J. Physiol. **231:** 1371–1376, 1976.
1130. STEIN, O., SANGER, I., AND STEIN, Y.: Colchicine-induced inhibition of lipoprotein and protein secretion into the serum and lack of interference with secretion of biliary phospholipids and cholesterol by rat liver in vivo. J. Cell Biol. **62:** 90–103, 1974.
1131. STEINBERG, S. E., CAMPBELL, C. L., AND HILLMAN, R. S.: Kinetics of the normal folate enterohepatic cycle. J. Clin. Invest. **64:** 83–88, 1979.
1132. STEINBERG, S. E., CAMPBELL, C. L., AND HILLMAN, R. S.: Effect of alcohol on hepatic secretion of methylfolate ($CH_3H_4PteGlu_1$) into bile. Biochem. Pharmacol. **30:** 96–98, 1981.
1133. STELLA, V. J., AND CHU, C. K.: Effects of short-term exposure to polychlorinated biphenyls on first pass metabolism of pentobarbital in rats. J. Pharmaceut. Sci. **69:** 1279–1282, 1980.
1134. STENSON, R. E., CONSTANTINO, R. T., AND HARRISON, D. C.: Interrelationships of hepatic blood flow, cardiac output and blood levels of lidocaine in man. Circulation **43:** 205–211, 1971.
1135. STERNLIEB, I.: Functional implications of human portal and bile ductular ultrastructure. Gastroenterology **63:** 321–327, 1972.
1136. STERNLIEB, I.: Copper and the liver. Gastroenterology **78:** 1615–1628, 1980.
1137. STIEHL, A., BECKER, M., CZYGAN, P., FROHLING, W., KOMMERELL, B., AND ROTTHAUWE, H. W.: Bile acids and their sulphated and glucuronidated derivatives in bile, plasma, and urine of children with intrahepatic cholestasis: Effects of phenobarbital treatment. Eur. J. Clin. Invest. **10:** 307–316, 1980.
1138. Stiehl, A., Czygan, P., Kommerell, B., Weis, H. J., and Holtermuller, K. H.: ursodeoxycholic acid versus chenodeoxycholic acid: Comparison of their effects on bile acid and bile lipid composition in patients with cholesterol gallstones. Gastroenterology **75:** 1016–1020, 1978.
1139. STOCKERT, R. J., GARTNER, U., MORELL, A. G., AND WOLKOFF, A. W.: Effects of receptor-specific antibody on the uptake of desialylated glycoproteins in the isolated perfused rat liver. J. Biol. Chem. **255:** 3830–3831, 1980.
1140. STOCKERT, R. J., HOWARD, D. J., MORELL, A. G., AND SCHEINBERG, I. H.: Functional segregation of hepatic receptors for asialoglycoproteins during endocytosis. J. Biol. Chem. **255:** 9028–9029, 1980.
1141. Stoeckel, K., McNamara, P. J., McLean, A. J., duSouich, P., Lalka, D., and Gibaldi, M.: Nonlinear pharmacokinetics of indocyanine green in the rabbit and rat. J. Pharmacokin. Biopharm. **8:** 483–496, 1980.
1142. STORSTEIN, L.: Studies on digitalis. III. Biliary excretion and enterohepatic circulation of digitoxin and its cardioactive metabolites. Clin. Pharmacol. Ther. **17:** 313–320, 1975.
1143. STRAMENTINOLI, G., DIPADOVA, C., GUALANO, M., ROVAGNATI, P., AND GALLI-KIENLE, M.: Ethynylestradiol-induced impairment of bile secretion in the rat: Protective effects of S-adenosyl-l-methionine and its implication in estrogen metabolism. Gastroenterology **80:** 154–158, 1981.
1144. STRAMENTINOLI, G., GUALANO, M., AND DIPADOVA, C.: Effect of S-adenosyl-L-methionine on ethynylestradiol-induced impairment of bile flow in female rats. Experientia (Basel) : 1361–1362, 1977.
1145. STRANGE, R. C., CHAPMAN, B. T., JOHNSTON, J. D., NIMMO, I. A., AND PERCY-ROBB, I. W.: Partitioning of bile acids into subcellular organelles and the in vivo distribution of bile acids in rat liver. Biochim. Biophys. Acta **573:** 535–545, 1979.
1146. STRANGE, R. C., NIMMO, I. A., AND PERCY-ROBB, I. W.: Studies in the rat on the hepatic subcellular distribution and biliary excretion of lithocholic acid. Biochim. Biophys. Acta **588:** 70–80, 1979.
1147. STRASBERG, S. M.: Effect of ethanol on formation of bile. Alcoholism: Clin. Exp. Res. **5:** 119–124, 1981.
1148. STRASBERG, S. M., ILSON, R. G., SIMINOVITCH, K. A., BRENNER, D., AND PALOHEIMO, J. E.: Analysis of the components of bile flow in the rhesus monkey. Am. J. Physiol. **228:** 115–121, 1975.
1149. STRASBERG, S. M., KAY, R. M., ILSON, R. G., PETRUNKA, C. N., AND PALOHEIMO, J. E.: Taurolithocholic acid and chlorpromazine cholestasis in the rhesus monkey. Can. J. Physiol. Pharmacol. **57:** 1138–1147, 1979.
1150. STRASBERG, S. M., SIMINOVITCH, K. A., AND ILSON, R. G.: Bile production in fasted and fed primates. Ann. Surg. **180:** 356–363, 1974.
1151. STRUM, W. B., AND LIEM, H. H.: Hepatic uptake, intracellular accumulation and biliary secretion of 5-methyltetrahydrofolate. Res. Commun. Chem. Path. Pharmacol. **30:** 493–507, 1980.
1152. SUTHERLAND, S. D.: The intrinsic innervation of the liver. Rev. Int. Hepatol. **15:** 569–578, 1965.
1153. SUTOR, D. J., AND WOOLEY, S. E.: The nature and incidence of gallstones containing calcium. Gut **14:** 215–220, 1973.
1154. SUZUKI, H., AND WADA, O.: Role of liver lysosomes in uptake and biliary excretion of maganese in mice. Environ. Res. **26:** 521–528, 1981.
1155. SWANSON, C. H., AND SOLLOMON, A. K.: Evidence for Na^+-H^+ exchange in the rabbit pancreas. Nature New Biol. **236:** 183–184, 1972.
1156. SWEENEY, G. D.: Functional heterogeneity among liver cells: Implications for drug toxicity and metabolism. Trends Pharmacol. Sci. **2:** 141–144, 1981.
1157. SWELL, L., ENTENMAN, C., LEONG, G. F., AND HOLLOWAY, R. J.: Bile acids and lipid metabolism. IV. Influence of bile acids on biliary and liver organelle phospholipids and cholesterol. Am. J. Physiol. **215:** 1390–1396, 1968.
1158. TAKEDA, S., AND ABURADA, M.: The choleretic mechanism of coumarin compounds and phenolic compounds. J. Pharm. Dyn. **4:** 724–734, 1981.
1159. Takeda, S., Endo, T., and Aburada, M.: Pharmacological studies on iridoid compounds. III. The choleretic mechanism of iridoid compounds. J. Pharm. Dyn. **4:** 612–6623, 1981.
1160. TANABE, T., PRICER, W. E., JR., AND ASHWELL, G.: Subcellular membrane topology and turnover of a rat hepatic binding protein specific for asialoglycoprotein. J. Biol. Chem. **254:** 1038–1043, 1979.
1161. TANTURI, C. A., AND IVY, A. C.: On the existence of secretory nerves in the vagi for and the reflex excitation and inhibition of bile secretion. Am. J. Physiol. **121:** 270–283, 1938.
1162. TAVOLONI, N.: Effect of K-strophanthin on bile secretion and hepatic perfusion in the isolated rat. Proc. Soc. Exp. Biol. Med. **160:** 463–467, 1979.
1163. TAVOLONI, N., AND GUARINO, A. M.: Does adriamycin undergo an enterohepatic circulation? Proc. Soc. Exp. Biol. Med. **169:** 41–46, 1982.
1164. TAVOLONI, N., REED, J. S., AND BOYER, J. L.: Hemodynamic effects on determinants of bile secretion in isolated rat liver. Am. J. Physiol. **234:** E584–E592, 1978.
1165. TAVOLONI, N., REED, J. S., AND BOYER, J. L.: Effect of chlorpromazine on hepatic clearance and excretion of bile acids by the isolated perfused rat liver. Proc. Soc. Exp. Biol. Med. **170:** 486–492, 1982.
1166. TAVOLONI, N., REED, J. S., HRUBAN, Z., AND BOYER, J. L.: Effect of chlorpromazine on hepatic perfusion and bile secretory function in the isolated perfused rat liver. J. Lab. Clin. Med. **94:** 726–741, 1979.
1167. TAYLOR, B. M., AND SUN, F. F.: Tissue distribution and biliary excretion of prostacyclin metabolites in the rat. J. Pharmacol. Exp. Ther. **214:** 24–30, 1980.
1168. TAYLOR, W.: The excretion of steroid hormone metabolites in bile and feces. Vitam. Horm. **29:** 201–285, 1971.
1169. TERAO, T., AND OWEN, C. A., JR.: Nature of copper compounds in liver supernate and bile of rats: Studies with ^{67}Cu. Am. J. Physiol. **224:** 682–686, 1973.
1170. TERHAAG, B., SCHERBER, A., SCHAPS, P., AND WINKLER, H.: The distribution of lithium into cerebrospinal fluid, brain tissue and bile in man. Int. J. Clin. Pharmacol. Biopharm. **16:** 333–335, 1978.
1171. TERRIS, S., HOFMANN, C., AND STEINER, D. F.: Mode of uptake and degradation of ^{125}I-labelled insulin by isolated hepatocytes and H4 hepatoma cells. Can. J. Biochem. **57:** 459–468, 1979.
1172. TERRIS, S., AND STEINER, D. F.: Binding and degradation of ^{125}I-insulin by rat hepatocytes. J. Biol. Chem. **250:** 8389–8398, 1975.
1173. Thistle, J. L., and Hofmann, A. F.: Efficacy and specificity of chenodeoxycholic acid therapy for dissolving gallstones. N. Engl. J. Med. **289:** 655–659, 1973.
1174. THOMAS, P., AND SUMMERS, J.: The biliary excretion of circulating asialoglycoproteins in the rat. Biochim. Biophys. Res. Commun. **80:** 335–339, 1978.
1175. THOMPSON, T. N., AND KLAASSEN, C. D.: Presystemic elimination of manganese in rats. Toxicol. Appl. Pharmacol. **64:** 236–243, 1982.
1176. THOMPSON, T. N., AND KLAASSEN, C. D.: Presystemic elimination of diethylstilbestrol by rat liver. Toxicologist **2:** 505, 1982.
1177. THOMSEN, O. O., AND LARSEN, J. A.: Comparison of vanadate and ouabain

effects on liver hemodynamics and bile production in the perfused rat liver. J. Pharmacol. Exp. Ther. **221:** 197–205, 1982.
1178. THUREBORN, E.: Human hepatic bile. Composition changes due to altered enterohepatic circulation. Acta Chir. Scand. **303:** (suppl.): 1–63, 1962.
1179. THURMAN, R. G., AND KAUFFMAN, F. C.: Factors regulating drug metabolism in intact hepatocytes. Pharmacol. Rev. **31:** 229–251, 1980.
1180. TICHY, M., AND CIKRT, M.: Manganese transfer into the bile in rats. Arch. Toxicol. **29:** 51–58, 1972.
1181. TICHY, M., CIKRT, M., AND HAVRDOVA, J.: Manganese binding in rat bile. Arch. Toxicol. **30:** 227–236, 1973.
1182. TICHY, M., HOREJSI, M., AND CIKRT, M.: Influence of spironolactone on the mercury biliary excretion mechanism in rats. Toxicol. Lett. **3:** 343–348, 1979.
1183. TIRIBELLI, C., LUNAZZI, G., LUCIANI, M., PANFILI, E., GAZZIN, B., LIUT, G., SANDRI, G., AND SOTTOCASA, G.: Isolation of a sulfobromophthalein-binding protein from hepatocyte plasma membrane. Biochim. Biophys. Acta **532:** 105–112, 1978.
1184. TOLMAN, K., G., SANNELLA, J. J., AND FRESTON, J. W.: Chemical structure of erythromycin and hepatotoxicity. Ann. Intern. Med. **81:** 58–60, 1974.
1185. TOTH, I., KENDLER, J., NAGPAUL, C., AND ZIMMERMAN, H. J.: Perfusion of the isolated rat liver with phenothiazines. Proc. Soc. Exp. Biol. Med. **140:** 1467–1471, 1972.
1186. TRAIGER, G. J., DEREPENTIGNY, L., AND PLAA, G. L.: Effect of inhibitors of protein and ribonucleic acid synthesis on the alteration in biliary bilirubin excretion and non-erythropoetically derived bilirubin synthesis in rats after α-naphthylisothiocyanate administration. Biochem. Pharmacol. **23:** 2845–2856, 1974.
1187. TRANBERG, K. G.: Hepatic uptake of insulin in man. Am. J. Physiol. **237:** E509–E518, 1979.
1188. TSUCHIYA, T., TERAKAWA, M., ISHIBASHI, K., NOGUCHI, H., AND KATO, R.: Disposition and enterohepatic circulation of diclofenac in dogs. Arzneim.-Forsch./Drug Res. **30:** 1650–1653, 1980.
1189. TUCHWEBER, B., AND GABBIANI, G.: Phalloidin-induced hyperplasia of actin fillaments in rat hepatocyes. *In* The Liver: Quantitative Aspects of structure and Function, ed. by R. Preisig, J. Bircher, and G. Paumgartner, pp. 84–90, Edito Cantor, Aulendorf, 1976.
1190. TURLEY, S. D.: Regulation of biliary cholesterol output in the rat: Dissociation from the rate of hepatic cholesterol synthesis, the size of the hepatic cholesteryl ester pool, and the hepatic uptake of chylomicron cholesterol. J. Lipid Res. **20:** 923–933, 1979.
1191. TURLEY, S. D., AND DIETSCHY, J. M.: Regulation of biliary cholesterol output in the rat: dissociation from the rate of cholesterol synthesis and the size of the cholesterol ester pool in the liver. Gastroenterology **74:** 1106, 1978.
1192. TURNBERG, L. A., BIEBERDORF, F. A., MORAWSKI, S. G., AND FORDTRAM, J. S.: Interrelationships of chloride, bicarbonate, sodium and hydrogen transport in human ileum. J. Clin. Invest. **49:** 557–567, 1970.
1193. UNGER, P. D., MEHENDALE, H. M., AND HAYES, A. W.: Hepatic uptake and disposition of aflatoxin B_1 in isolated perfused rat liver. Toxicol. Appl. Pharmacol. **41:** 523–534, 1977.
1194. UPSON, D. W., GRONWALL, R. R., AND CORNELIUS, C. E.: Maximal hepatic excretion of bilirubin in sheep. Proc. Soc. Exp. Biol. Med. **134:** 9–12, 1970.
1195. UTILI, R., ABERNATHY, C. O., AND ZIMMERMAN, H. J.; Cholestatic effects of *Escherichia coli* endotoxin on the isolated perfused rat liver. Gastroenterology **70:** 248–253, 1976.
1196. UTILI, R., ABERNATHY, C., O., AND ZIMMERMAN, H. J.: Studies on the effect of *Escherichia coli* endotoxin on canalicular bile formation in the isolated perfused rat liver. J. Lab. Clin. Med. **89:** 471–482, 1977.
1197. UTILI, R., ABERNATHY, C. O., ZIMMRMAN, H. J., AND GAETA, G. B.: Hepatic excretory function in the endotoxin-tolerant rat. Proc. Soc. Exp. Biol. Med. **161:** 554–557, 1979.
1198. VAILLE, CH., DEBRAY, CH., ROZE, C., AND SOUCHARD, M.: Action of carbutamide upon the biliary flow of the rat. J. Pharmacol. (Paris) **3:** 449–458, 1972.
1199. VANBERKEL, T. J. C., AND VANTOL, A.: Role of parenchymal and non-parenchymal rat liver cells in the uptake of cholesterolester-labeled serum lipoproteins. Biochem. Biophys. Res. Commun. **89:** 1097–1101, 1979.
1200. VANBEZOOIJEN, C. F. A., GRELL, T., AND KNOOK, D. L.: Bromsulfophthalein uptake by isolated liver parenchymal cells. Biochem. Biophys. Res. Commun. **69:** 354–361, 1976.
1201. VANCAMPEN, D. R., AND KOWALSKI, T. J.: Studies on zinc absorption: ^{65}Zn binding by homogenates of rat intestinal mucosa. Proc. Soc. Exp. Biol. Med. **136:** 294–297, 1971.
1202. VANDYKE, R. W., STEPHENS, J. E., AND SCHARSCHMIDT, B. F.: Effects of ion substitution on bile acid-dependent and -independent bile formation by rat liver. J. Clin. Invest. **70:** 505–517, 1982.
1203. VANSTEENBERGEN, W., AND FEVERY, J.: Maximal biliary secretion of bilirubin in the anesthetized rat: Dependence on UDP-glucuronosyltransferase activity. Clin. Sci. **62:** 521–528, 1982.
1204. VARGA, F., FISCHER, E., AND SZILY, T. S.: Biliary excretion of bromsulphthalein and glutathione conjugate of bromsulphthalein in rats pretreated with diethyl maleate. Biochem. Pharmacol. **23:** 2617–2623, 1974.
1205. VERDY, M., TETREAULT, L., MURPHY, W., AND PERRON, L.: Effect of methandrostenolone on blood lipids and liver function tests. Can. Med. Assoc. J. **98:** 397–401, 1968.
1206. Vest, M. F.: Conjugation of sulfobromophthalein in newborn infants and children. J. Clin. Invest. **41:** 1013–1020, 1962.
1207. VLAHCEVIC, Z. R., BELL, C. C., JR., BUHAC, I., FARRAR, J. T., AND SWELL, L.: Diminished bile acid pool size in patients with gallstones. Gastroenterology **59:** 165–173, 1970.
1208. VLAHCEVIC, Z. R., BELL, C. C., JR., AND SWELL, L.: Significance of the liver in the production of lithogenic bile in man. Gastroenterology. **59:** 62–69, 1970.
1209. VONBAHR, C., BORGA, O., FELLENIUS, E., AND ROWLAND, M.: Kinetics of nortriptyline (NT) in rats in vivo and in the isolated perfused liver: Demonstration of a "first pass disappearance" of NT in the liver. Pharmacology **9:** 177–186, 1973.
1210. VONK, R. J., DANHOF, M., COENRAADS, T., VAN DOORN, A. B. D., KEULEMANS, K., SCAF, A. H. J., AND MEIJER, D. K. F.: Influence of bile salts on hepatic transport of dibromosulphthalein. Am. J. Physiol. **237:** E524–E534, 1979.
1211. VONK, R. J., JEKEL, P., AND MEIJER, D. K. F.; Choleresis and hepatic transport mechanisms. II. Influence of bile salt choleresis and biliary micelle binding on biliary excretion of various organic anions. Naunyn-Schmiedeberg's Arch. pharmacol. **290:** 375–387, 1975.
1212. Vonk, R. J., Jekel, P. A., Meijer, D. K. F., and Hardonk, M. J.: Transport of drugs in isolated hepatocytes. The influence of bile salts. Biochem. Pharmacol. **27:** 397–405, 1978.
1213. Vonk, R. J., Scholtens, E., Keulemans, G. T. P., and Meijer, D. K. F.: Choleresis and hepatic transport mechanisms. IV. Influence of bile salt choleresis on the hepatic transport of the organic cations, D-tubocurarine and N_4-acetyl procainamide ethobromide. Naunyn-Schmiedeberg's Arch. Pharmacol. **302:** 1–9, 1978.
1214. Vonk, R. J., Scholtens, E., and Strubble, J. H.: Biliary excretion of dibromosulphthalein in the freely moving unanesthetized rat: Circadian variation and effects of deprivation of food and pentobarbital anaesthesia. Clin. Sci. Mol. Med. **55:** 399–406, 1978.
1215. VONK, R. J., TUCHWEBER, B., MASSE, D., PEREA, A., AUDET, M., ROY, C. C., AND YOUSEF, I. M.: Intrahepatic cholestasis induced by allo monohydroxy bile acid in rats. Gastroenterology **81:** 242–249, 1981.
1216. Vonk, R. J., Van Doorn, A. B. D., Scaf, A. H. J., and Meijer, D. K. F.: Choleresis and hepatic transport mechanisms. III. Binding of ouabain and K-strophanthoside to biliary micelles and influence of choleresis on their biliary excretion. Naunyn-Schmiedeberg's Arch. Pharmacol. **300:** 173–177, 1977.
1217. VONK, R. J., VAN DOORN, A. B. D., AND STRUBBLE, J. H.: Bile excretion and bile composition in the freely moving unanesthetized rat with a permanent biliary drainage: Influence of food intake on bile flow. Clin. Sci. Mol. Med. **55:** 253–259, 1978.
1218. VONK, R. J., V. D. VEEN, H., PROP, G., AND MEIJER, D. K. F.: The influence of taurocholate and dehydrocholate choleresis on plasma disappearance and biliary excretion of indocyanine green in the rat. Naunyn-Schmiedeberg's Arch. Pharmacol. **282:** 401–410, 1974.
1219. VORE, M., BAUER, J., AND PASCUCCI, V.: The effect of pregnancy on the metabolism of (^{14}C)phenytoin in the isolated perfused rat liver. J. Pharmacol. Exp. Ther. **206:** 439–447, 1978.
1220. VORE, M., AND MONTGOMERY, C.: The effect of estradiol-17β treatment on the metabolism and biliary excretion of phenytoin in the isolated perfused rat liver and in vivo. J. Pharmacol. Exp. Ther. **215:** 71–76, 1980.
1221. VORE, M., AND SOLIVEN, E.: Hepatic estrone and estradiol glucuronyltransferase activity in pregnancy. Drug Metab. Dispos. **7:** 247–251, 1979.
1222. Vore, M., Soliven, e., and Blunden, M.: the effect of pregnancy on the biliary excretion of (^{14}C)phenytoin in the rat. J. Pharmacol. Exp. Ther. **208:** 257–262, 1979.
1223. WACHSTEIN, M.: Enzymatic histochemistry of the liver. Gastroenterology **37:** 525–537, 1959.
1224. WAGNER, C. I., TROTMAN, B. W., AND SOLOWAY, R. D.: Kinetic analysis of biliary lipid excretion in man and dog. J. Clin. Invest. **57:** 473–477, 1976.
1225. WAHLLANDER, A., AND SIES, H.: Glutathione S-conjugate formation from 1-chloro-2,4-dinitrobenzene and biliary S-conjugate excretion in the perfused rat liver. Eur. J. Biochem. **96:** 441–446, 1979.
1226. WALL, D. A., AND HUBBARD, A. L.: Galactose-specific recognition system of mammlian liver: Receptor distribution on the hepatocyte cell surface. J. Cell Biol. **90:** 687–696, 1981.
1227. WALL, D. A., WILSON, G., AND HUBBARD, A. L.: The galactose-specific recognition system of mammalian liver: The route of ligand internalization of rat hepatocytes. Cell **21:** 79–93, 1980.
1228. WALLI, A. K., WIELAND, E., AND WIELAND, TH.: Phalloidin uptake by the liver of cholestatic rats in vivo, in isolated perfused liver and isolated hepatocytes. Naunyn-Schmiedeberg's Arch. Pharmacol. **316:** 257–261, 1981.
1229. WALLIN, J. D., CLIFTON, G., AND KAPLOWITZ, N.: The effect of phenobarbital, probenecid and diethyl maleate on the pharmacokinetics and biliary excretion of ethacrynic acid in the rat. J. Pharmacol. Exp. Ther. **205:** 471–479, 1978.
1230. WANNAGAT, F.-J., ADLER, R. D., AND OCKNER, R. K.: Bile acid-induced

increase in bile acid-independent flow and plasma membrane NaK-ATPase activity in rat liver. J. Clin. Invest. **61:** 297–307, 1978.
1231. WANSON, J.-C., DROCHMANS, P., MAY, C., PENASSE, W., AND POPOWSKI, A.: Isolation of centrolobular and perilobular hepatocytes after phenobarbital treatment. J. Cell Biol. **66:** 23–41, 1975.
1232. WARE, A. J., CAREY, M. C., AND COMBES, B.: Solution properties of sulfobromophthalein sodium (BSP) compounds alone and in association with sodium taurocholate (TC). J. Lab. Clin. Med. **87:** 443–456, 1976.
1233. WATKINS, J., B., GREGUS, Z., THOMPSON, T. N., AND KLAASSEN, C. D.: Induction studies on the functional heterogeneity of UDP-glucuronosyltransferases. Toxicol. Appl. Pharmacol. **64:** 439–446, 1982.
1234. WATKINS, J. B., AND KLAASSEN, C. D.: Choleretic effect of valproic acid in the rat. Hepatology **1:** 341–347, 1981.
1235. WATKINS, J. B., AND KLAASSEN, C. D.: Effect of repeated oral administration of taurocholate on hepatic excretory function in the rat. J. Pharmacol. Exp. Ther. **218:** 182–187, 1981.
1236. WATKINS, J. B., AND KLAASSEN, C. D.: Effect of inducers and inhibitors of glucuronidation on the biliary excretion and choleretic action of valproic acid. J. Pharmacol. Exp. Ther. **220:** 305–310, 1982.
1237. WATKINS, J. B., AND KLAASSEN, C. D.: Induction of UDP-glucuronosyltransferase activities in Gunn, heterozygous and Wistar rat livers by pregnenolone-16α-carbonitrile. Drug Metab. Dispos. **10:** 590–594, 1982.
1238. WATKINS, J. B., AND KLAASSEN, C. D.: Determination of hepatic uridine 5′-diphosphoglucuronic acid concentration with diethylstilbestrol. J. Pharmacol. Methods **7:** 145–151, 1982.
1239. WATKINS, J. B., AND KLAASSEN, C. D.: Chemically-induced alteration of UDP-glucuronic acid concentration in rat liver. Drug Metab. Dispos. **11:** 37–40, 1983.
1240. WEBB, J. M., FONDA, M., AND BROUWER, E. A.: Metabolism and excretion patterns of fluorescein and certain halogenated fluorescein dyes in rats. J. Pharmacol. Exp. Ther. **137:** 141–147, 1962.
1241. WEBB, M.: Binding of cadmium ions by rat liver and kidney. Biochem. Pharmacol. **21:** 2751–2765, 1972.
1242. WEBB, M.: Protection by zinc against cadmium toxicity. Biochem. Pharmacol. **21:** 2767–2771, 1972.
1243. WEINBREN, K., AND BILLING, B. H.: Hepatic clearance of bilirubin as an index of cellular function in the regenerating rat liver. Br. J. Exp. Pathol. **37:** 199–204, 1956.
1244. WEINER, I. M., AND LACK, L.: Bile salt absorption; enterohepatic circulation. *In* Handbook of Physiology, Section 6: Alimentary Canal, vol. 3, pp. 1439–1455, American Physiology Society, Washington, DC, 1968.
1245. WHEELER, H. O.: Water and electrolytes in bile. *In* Handbook of Physiology, Section 6: Alimentary Canal, vol. 5, pp. 2409–2431, American Physiology Society, Washington, DC, 1968.
1246. WHEELER, H. O.: Secretion of bile acids by the liver and their role in the formation of hepatic bile. Arch. Intern. Med. **130:** 533–541, 1972.
1247. WHEELER, H. O.: The choleretic effect of iodipamide. J. Clin. Invest. **55:** 528–535, 1975.
1248. WHEELER, H. O., CRANSTON, W. I., AND MELTZER, J. I.: Hepatic uptake and biliary excretion of indocyanine green in the dog. Proc. Soc. Exp. Biol. med. **99:** 11–14, 1958.
1249. WHEELER, H. O., EPSTEIN, R. M., ROBINSON, R. R., AND SNELL, E. S.: Hepatic storage and excretion of sulfobromophthalein sodium in the dog. J. Clin. Invest. **39:** 236–247, 1960.
1250. WHEELER, H. O., AND KING, K. K.: Biliary excretion of lecithin and cholesterol in the dog. J. Clin. Invest. **51:** 1337–1350, 1972.
1251. WHEELER, H. O., AND MANCUSI-UNGARO, P. L.: Role of bile ducts during secretin choleresis in dogs. Am. J. Physiol. **210;** 1153–1159, 1966.
1252. WHEELER, H. O., MELTZER, J. I., AND BRADLEY, S. E.: Biliary transport and hepatic storage of sulfobromophthalein sodium in the unanesthetized dog, in normal man, and in patients with hepatic disease. J. Clin. Invest. **39:** 1131–1144, 1960.
1253. WHEELER, H. O., AND RAMOS, O. L.: Determinants of the flow and composition of bile in the unanesthetized dog during constant infusions of sodium taurocholate. J. Clin. Invest. **39:** 161–170, 1960.
1254. WHEELER, H. O., ROSS, E. D., AND BRADLEY, S. E.: Canalicular bile production in dogs. Am. J. Physiol. **214:** 866–874, 1968.
1255. WHELAN, G., AND COMBES, B.: Phenobarbital-enhanced biliary excretion of administered unconjugated and conjugated sulfobromophthalein (BSP) in the rat. Biochem. Pharmacol. **24:** 1283–1986, 1975.
1256. WHELAN, G., HOCH, J., AND COMBES, B.: A direct assessment of the importance of conjugation for biliary transport of sulfobromophthalein sodium. J. Lab. Clin. Med. **75:** 542–557, 1970.
1257. WHITE, I. N. H.: Biliary excretion of green pigments produced by norethindrone in the rat. Biochem. Pharmacol. **31:** 1337–1342, 1982.
1258. WHITSETT, T. L., DAYTON, P. G., AND MCNAY, J. L.: The effect of hepatic blood flow on the hepatic removal rate of oxyphenbutazone in the dog. J. Pharmacol. Exp. Ther. **177:** 246–255, 1971.
1259. WIELAND, H., AND DANE, E.: Untersuchungen uber die konstitution der gallensauren XXXIX Mitteilung zur Kenntnis der 12-oxycholansaure. Hoppe-Seyler's Z. Physiol. Chem. **210:** 268–277, 1932.
1260. WIESNER, R. H., KUMAR, R., SEEMAN, E., AND GO, V. L. W.: Enterohepatic physiology of 1,25-dihydroxyvitamin D_3 metabolties in normal man. J. Lab. Clin. Med. **96:** 1094–1100, 1980.
1261. WILKINSON, G. R.: Pharmacokinetics of drug disposition: Hemodynamic consideration. Annu. Rev. Pharmacol. **15:** 11–27, 1975.
1262. WILKINSON, G. R., AND SCHENKER, S.: Commentary: Effects of liver disease and drug disposition in man. Biochem. Pharmacol. **25:** 2675–2681, 1976.
1263. WILKINSON, G. R., AND SHAND, D. G.: Commentary: A physiological approach to hepatic drug clearance. Clin. Pharmacol. Ther. **18:** 377–390, 1975.
1264. WILLIAMS, R. L., AND MAMELOK, R. D.: Hepatic disease and drug pharmacokinetics. Clin. Pharmacokinet. **5:** 528–547, 1980.
1265. WILLIAMS, R. T.: Detoxication Mechanisms, Chapman and Hall, London, 1947.
1266. WILLIAMS, R. T., MILLBURN, P., AND SMITH, R. L.: The influence of enterohepatic circulation on toxicity of drugs. Ann. N.Y. Acad. Sci. **123:** 110–124, 1965.
1267. Williamson, B. W. A., and Percy-Robb, I. W.: Contribution of biliary lipids to calcium binding in bile. Gastroenterology **78:** 696–702, 1980.
1268. WILLSON, R. A., HART, F. E., AND HEW, J. T.: Experimental hepatobiliary injury. Comparison of in vivo drug elimination with in vitro drug metabolizing enzyme capacity in the rat. Digest. Dis. Sci. **26:** 50–59, 1981.
1269. WILLSON, R. A., AND HART, J. R.: In vivo drug metabolism and liver lobule heterogeneity in the rat. Gastroenterology **81:** 563–569, 1981.
1270. WILSON, G.: Selective hepatic uptake of synthetic glycoproteins. Mannosaminated ribonuclease A dimer and serum albumin. J. Gen. Physiol. **74:** 495–509, 1979.
1271. WINGE, D. R., PREMAKUMAR, R., AND RAJAGOPALAN, K. V.: metal-induced formation of metallothionein in rat liver. Arch. Biochem. Biophys. **170:** 242–252, 1973.
1272. Winge, D. R., and Rajagopalan, K. V.: Purification and some properties of Cd-binding protein from rat liver. Arch. Biochem. Biophys. **153:** 755–762, 1972.
1273. WINKLER, K., BASS, L., KEIDING, S., AND TYGSTRUP, N.: The physiologic basis for clearance measurements in hepatology. Scand. J. Gastroent. **14;** 439–448, 1979.
1274. WITZLEBEN, C. L.: Bilirubin as a cholestatic agent: physiologic and morphologic observations. Am. J. Pathol. **62:** 181–194, 1971.
1275. WITZLEBEN, C. L., AND BOYCE, W. H.: Bilirubin as a cholestatic agent. III. Prevention of bilirubin-related cholestasis by sulfobromophthalein (BSP). Arch. Pathol. **99:** 492–495, 1975.
1276. WITZLEBEN, C. L., AND BOYCE, W. H.: Bilirubin as a cholestatic agent. IV. Effect of bilirubin and sulfobromophthalein (BSP) on biliary manganese excretion. Arch. Pathol. **99:** 496–498, 1975.
1277. WITZLEBEN, C. L., PITLICK, P., BERGMEYER, J., AND BENOIT. R.: Acute manganese overload. A new experimental model of intrahepatic cholestasis. Am. J. Pathol. **53:** 409–423, 1968.
1278. WOLEN, R. L., GRUBER, C. M., KIPLINGER, G. F., AND SCHOLZ, N. E.: Concentration of propoxyphene in human plasma following oral, intramuscular, and intravenous administration. Toxicol. Appl. Pharmacol. **19:** 480–492, 1971.
1279. WOLKOFF, A. W.: The glutathione S-transferases; Their role in the transport of organic anions from blood to bile. Int. Rev. Physiol. **21:** 151–169, 1980.
1280. WOLKOFF, A. W., AND CHUNG, C. T.: Identification, purification, and partial characterization of an organic anion binding protein from rat liver cell plasma membrane. J. Clin. Invest. **65:** 1152–1161, 1980.
1281. WOLKOFF, A. W., GORESKY, C. A., SELLIN, J., GATMAITAN, Z., AND ARIAS, I. M.: Role of ligandin in transfer of bilirubin from plasma into liver. Am. J. Physiol. **236:** E638–E648, 1979.
1282. WOLKOFF, A. W., KETLEY, J. N., WAGGONER, J. G., BERK, P. D., AND JAKOBY, W. B.: Hepatic accumulation and intracellular binding of conjugated bilirbuin. J. Clin. Invest. **61:** 142–149, 1978.
1283. WOOD, A. J. J., VESTAL, R. E., WILKINSON, G. R., BRANCH, R. A., AND SHAND, D. G.: Effect of aging and cigarette smoking on antipyrine and indocyanine green elimination. Clin. Pharmacol. Ther. **26:** 16–20, 1979.
1284. WOSILAIT, W. D.: The effect of BSP and rifamycin on the excretion of warfarin in the bile of the rat. Gen. Pharmacol. **8:** 349–353, 1977.
1285. WOSILAIT, W. D., RYAN, M. P., AND BYINGTON, K. H.: Uptake of anticoagulants by isolated rat hepatocytes. Drug Metab. Dispos. **9:** 80–84, 1981.
1286. WYNGAARDEN, J. B., PETERSON, R. E., AND WOLFF, A. R.: Physiologic disposition of radiometabolites of hydrocortisone-4-C^{14} in the rat and guinea-pig. J. Biol. Chem. **212:** 963–972, 1955.
1287. YANG, K. H., CROFT, W. A., AND PETERSON, R. E.: Effects of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin on plasma disappearance and biliary excretion of foreign compounds in rats. Toxicol. Appl. Pharmacol. **40:** 485–496, 1977.
1288. YASUHARA, H., DUJOVNE, C. A., UEDA, I., AND ARAKAWA, K.: Hepatotoxicity and surface activity of tricyclic antidepressants in vitro. Toxicol. Appl. Pharmacol. **47:** 47–54, 1979.
1289. YASUHARA, H., DUJOVNE, C. A., AND UEDA, I.: Relationship between surface activity and toxicity to Chang liver cultures of tricyclic antidepressants. Pharmacology **18:** 95–102, 1979.
1290. YIP, C. C., YEUNG, C. W. T., AND MOULE, M. L.: Photoaffinity labeling

of insulin receptor proteins of liver plasma membrane preparations. Biochemistry **19**: 70–76, 1980.

1291. YOUNG, S. P., AND AISEN, P.: Transferrin receptors and the uptake and release of iron by isolated hepatocytes. Hepatology **1**: 114–119, 1981.
1292. YOUSEF, I. M., TUCHWEBER, B., VONK, R. J., MASSE, D., AUDET, M., AND ROY, C. C.: Lithocholate cholestasis-sulfated glycolithocholate-induced intrahepatic cholestasis in rats. Gastroenterology **80**: 233–241, 1981.
1293. YOUSEF, I. M., TUCHWEBER, B., WEBER, A., LEE, D., AND ROY, C. C.: Prevention of lithocholate cholestasis by inhibition of protein synthesis. Hepatology **2**: 729, 1982.
1294. ZATERKA, S., AND GROSSMAN, M. I.: The effect of gastrin and histamine on secretion of bile. Gastroenterology **50**: 500–505, 1966.
1295. ZIEGLER, K.: Isolation of hepatocytes from newborn rats. Arch. Toxicol. **44**: 99–105, 1980.
1296. ZIEGLER, K., PETZINGER, E., GRUNDMANN, E., AND FRIMMER, M.: Decreased sensitivity of isolated hepatocytes from baby rats, from regenerating and from poisoned livers against phalloidin. Naunyn-Schmiedeberg's Arch. Pharmacol. **306**: 295–300, 1979.
1297. ZIMMERMAN, H. J.: Hepatic injury caused by therapeutic agents. *In* The Liver: Normal and Abnormal Functions, Part A, ed. by F. F. Becker, pp. 225–302, Marcel Dekker, New York, 1974.
1298. ZIMMERMAN, H. J.: Hepatotoxicity. Appleton-Century-Croft, New York, 1978.
1299. ZIMMERMAN, H. J., ABERNATHY, C. O., LUKACS, L., AND EZEKIEL, M.: Effects of tricrynafen on hepatic excretory function in the isolated perfused rat liver. Hepatology **2**: 255–257, 1982.
1300. ZSIGMOND, G., AND SOLYMOSS, B.: Increased canalicular bile production induced by pregnenolone-16α-carbonitrile, spironolactone and cortisol in rats. Proc. Soc. Exp. Biol. Med. **145**: 631–635, 1974.