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**Mechanisms of Bile Formation, Hepatic Uptake, and

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Biliary Excretion** blogy and Experimental Therapeutics
Biliary Excretion
Biliary Excretion
BILIARSEN' and JOHN B. WATKINS II **Biliary Excretion**
CURTIS D. KLAASSEN^{*} and JOHN B. WATKINS III

EXCFELION
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Program, Indiana Universi

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IX. Concluding remarks

BILIARY excretion of xenobiotics is a complex process

volving uptake into liver cells, intracellular sequestra-EXECUTE INTERT EXECUTE IN THE INTERT SILLARY excretion of xenobiotics is a complex proprior
involving uptake into liver cells, intracellular sequestion and/or biotransformation, and transport into l BILIARY excretion of xenobiotics is a complex process
involving uptake into liver cells, intracellular sequestra-
tion and/or biotransformation, and transport into bile.
A description of liver morphology and the possible m BILIARY excretion of xenobiotics is a complex proce
involving uptake into liver cells, intracellular sequestri
tion and/or biotransformation, and transport into bil
A description of liver morphology and the possible mec
an BILIARY excretion of xenobiotics is a complex proce-
involving uptake into liver cells, intracellular sequest-
tion and/or biotransformation, and transport into bi
A description of liver morphology and the possible meanism 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 un tion and/or biotransformation, and transport into b
A description of liver morphology and the possible me
anisms of bile formation is included to aid in the und
standing of how chemical and physiological factors aff
bile f 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. Ent anisms of bile formation is included to aid in the under-
standing of how chemical and physiological factors affect
bile flow, hepatic uptake, and biliary excretion. Entero-
hepatic circulation interferes with the biliary standing of how chemical and physiological factors affect in c
bile flow, hepatic uptake, and biliary excretion. Entero-
hepatic circulation interferes with the biliary elimination Hip
of xenobiotics from the body. The co bile flow, hepatic uptake, and biliary excretion. Entero-
hepatic circulation interferes with the biliary elimination Hip
of xenobiotics from the body. The considerable volume mo
of information that has accumulated in rece

view. is discussed in this com
I. Historical Aspects
have been considered to

Liver and bile have been considered to be important
determining temperament and health since the days 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 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 fou 1. 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 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 hu-
mors (b in determining temperament and health since the days
of the ancient Babylonian and Greek civilizations. In
Hippocratic medicine, bile was one of four cardinal hu-
mors (blood, phlegm, yellow bile from liver, black bile
fro of the ancient Babylonian and Greek civilizations. In
Hippocratic medicine, bile was one of four cardinal hu-
mors (blood, phlegm, yellow bile from liver, black bile
from stomach) which were thought to control the health
s

long duration were attributed to abnormalities in yellow BILE FORMATION, HEPATIC UPTAKE, A
tained a humoral view of disease; for example, fevers of little
long duration were attributed to abnormalities in yellow work
and black bile. In fact, the word melancholy is derived tion (BILE FORMATION, HEPATIC UPTAK
tained a humoral view of disease; for example, fevers of lit
long duration were attributed to abnormalities in yellow
and black bile. In fact, the word melancholy is derived tion
from the Gree 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) tained a humoral view of disease; for example, fevers of littllong duration were attributed to abnormalities in yellow wor
and black bile. In fact, the word melancholy is derived tion
from the Greek words, melas (black) an long duration were attributed
and black bile. In fact, therefore the Greek words, m
since mental depression vexcess of "black bile."
Scientific studies initiat d black bile. In fact, the word melancholy is derived tion the Greek words, melas (black) and chole (bile) of the seventeenth century cess of "black bile." bisologist. The seventeenth century statomist and physiologist, Re

from the Greek words, melas (black) and chole (bile) of since mental depression was thought to arise from an pexcess of "black bile."

Scientific studies initiated by the seventeenth century solutions and physiologist, Reg since mental depression was thought to arise from
excess of "black bile."
Scientific studies initiated by the seventeenth centu
anatomist and physiologist, Regnier de Graff, describ
the collection of bile and pancreatic ju mental fistulae. Then Schwann, in 1844, established the Scientific studies initiated by the seventeenth century strue
anatomist and physiologist, Regnier de Graff, described affliche
the collection of bile and pancreatic juice from experi-
mental fistulae. Then Schwann, in 1844 anatomist and physiologist, Regnier de Graff, described affliche collection of bile and pancreatic juice from experimental fistulae. Then Schwann, in 1844, established the hepuse of permanent biliary fistulae in dogs and B the collection of bile and pancreatic juice from experemental fistulae. Then Schwann, in 1844, established tuse of permanent biliary fistulae in dogs and Blondt, 1846, was the first to use a cannula (378). Much work the ni mental fistulae. Then Schwann, in 1844, established the huse of permanent biliary fistulae in dogs and Blondt, in w
1846, was the first to use a cannula (378). Much work in d:
the nineteenth century evaluated the physiolog 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 1846, was the first to use a cannula (378). Much work in dy
the nineteenth century evaluated the physiological chem-
istry of bile and its composition. Crude preparations of
bile salts were obtained by Thenard in 1807 and the nineteenth century evaluated the physiological chem-
istry 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 istry 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). Berzel 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 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,
Figreen-colored biliverdin and yellow bilirubin. not elucidated until the early 1930s (1259). Berzelius, in 1842, showed that bile pigment could exist in two forms, Higreen-colored biliverdin and yellow bilirubin. By the an 1890s, bile was considered to be a physiologica 1842, showed that bile pigment could exist in two forms, Hightgreen-colored biliverdin and yellow bilirubin. By the and 1890s, bile was considered to be a physiological secretion nutries are used as a very product containi green-colored biliverdin an
1890s, bile was considered t
necessary for digestive pro
well as an excretory produc
bile pigments (378, 1027).
Today the dominant ph 90s, bile was considered to be a physiological secretion α resessary for digestive processing of consumed fats as vell as an excretory product containing cholesterol and parameters (378, 1027). Today the dominant physi

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 th 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 th bile pigments (378, 1027).
Today the dominant physiological role of bile is
involvement in digestion and the intestinal absorpti
of fats. However, studies on the excretion of numero
endogenous and exogenous compounds have Today the dominant physiological role of bile is involvement in digestion and the intestinal absorptic of fats. However, studies on the excretion of numerolendogenous and exogenous compounds have demonstrated the importanc involvement in digestion and the intestinal absorption
of fats. However, studies on the excretion of numerou
endogenous and exogenous compounds have demon
strated the importance of biliary excretion in the elimi
nation of of fats. However, studies on the excretion of numerous
endogenous and exogenous compounds have demon-
strated the importance of biliary excretion in the elimi-
nation of chemicals from the body. In his manuscript,
Traité d 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 fa strated 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 me-
talli nation of chemicals from the body. In his manuscript, syntraité de Toxicologie Général (1813–1815), M. J. B. v
Orphila, the father of toxicology, noted that many me-
tallic poisons are extracted by the liver and are either Traité de Toxicologie Général (1813–1815), M. J. B.
Orphila, the father of toxicology, noted that many me-
tallic poisons are extracted by the liver and are either
excreted into bile or remain in the liver. Later, Claude
B Orphila, the father of toxicology, noted that many metallic poisons are extracted by the liver and are eithexcreted into bile or remain in the liver. Later, Claud Bernard observed that copper sulfate, potassium iodid and t tallic 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 excreted into bile or remain in the liver. Later, Claude sinus
Bernard observed that copper sulfate, potassium iodide, row
and turpentine spirits are found in bile soon after intra-
as the veloped a method to visualize the Bernard observed that copper sulfate, potassium iodide, row
and turpentine spirits are found in bile soon after intra-
venous administration. Then in 1866, Chrzonszczewsky
the
developed a method to visualize the biliary tr venous 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 quali-
 venous 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 quali-
 developed a method to visualize the biliary tree bases biliary excretion of two dyes, aniline red and is carmine (189). These early studies were generally tative and the quantitative significance of hepatitraction and excr liary excretion of two dyes, aniline red and indigo

rmine (189). These early studies were generally quali-

tive and the quantitative significance of hepatic ex-

action and excretion into bile remained obscure.

The dem

carmine (189). These early studies were generally quali-
tative and the quantitative significance of hepatic ex-
traction and excretion into bile remained obscure.
The demonstration in 1909 by Abel and Rowntree (1)
that s traction 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 a The demonstration in 1909 by Abel and Rowntree (1) that several phthalein dyes undergo extensive biliary the excretion led to the development of diagnostic tests for hepatic and biliary function. The radio-opaque dye, tetr 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
use 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). 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 sul-
fo tetraiodophenolphthalein, is excreted into bile and was
used to visualize the gallbladder by X-irradiation (413).
Meanwhile, Rosenthal and White (1002) introduced sul-
fobromophthalein (BSP) as a diagnostic test of liver
f used to visualize the gallbladder by X-irradiation (413).
Meanwhile, Rosenthal and White (1002) introduced sul-
fobromophthalein (BSP) as a diagnostic test of liver
function by measuring the rate of disappearance of the
dy Meanwhile, Rosenthal and White (1002) introduced sulfobromophthale
in (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 v fobromophthalein (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
stu 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
sim dye from plasma. BSP retent
of various forms of hepati
studies have been performe
of hepatic disposition and b
similar prototype chemicals.
The biliary elimination various forms of hepatic disease (724). Additional
udies have been performed to determine mechanisms
hepatic disposition and biliary excretion of BSP and
nilar prototype chemicals.
The biliary elimination of xenobiotics wa

Little during the first half of the twentieth century as
little during the first half of the twentieth century as
work was directed toward understanding urinary excre-WHT AND BILIARY EXCRETION
little during the first half of the twentieth century
work was directed toward understanding urinary excre-
tion (1265). From 1950, with the wide-scale introductie SIME, AND BILIARY EXCRETION 3

ittle during the first half of the twentieth century as

work was directed toward understanding urinary excre-

tion (1265). From 1950, with the wide-scale introduction

of myriad synthetic c little during the first half of the twentieth century as
work was directed toward understanding urinary excre-
tion (1265). From 1950, with the wide-scale introduction
of myriad synthetic chemicals (drugs, food additives,
 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 additive pest 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 xenobio of myriad synthetic chemicals (drugs, food additives, pesticides), the importance of bile as a channel of xeno-
biotic excretion was realized. Compounds of complex
structure and higher molecular weight have a greater
affin of myriad synthetic chemicals (drugs, food additives, pesticides), the importance of bile as a channel of xeno-
biotic excretion was realized. Compounds of complex
structure and higher molecular weight have a greater
affin pesticides), the importance of bile as a channel of xeno-
biotic excretion was realized. Compounds of complex
structure and higher molecular weight have a greater
affinity for elimination into bile than chemicals of lower
 biotic 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,
hepati 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
w 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 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 II. II. Morphological Perspectives of Biliary
II. Morphological Perspectives of Biliary
II. Morphological Perspectives of Biliary
II. Morphological Perspectives of Biliary
Excretion

Excretion

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 H. 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 Exeretion

Exeretion

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 **nutrient School 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 suppl 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
venule 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
 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 dive 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 branch 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 fibrou 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
(hepat 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 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
beco issue 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 II. Morphological Perspectives of Biliary

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 carr 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 vasc 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 s 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 t vascular trees is filled with hepatocytes that line the sinusoids, which are arranged tridimensionally and bur-
row 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). row 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 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 struc-
ture

tative and the quantitative significance of hepatic ex - histological sections is hexagonal with portal spaces at
traction and excretion into bile remained obscure.
The lobule can be viewed as a wheel with
The demonstrati 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 histologi sinusoids and with walls of hepatocytes (117).
Several seemingly conflicting concepts of liver struc-
ture are actually complementary. The classic lobule in
histological sections is hexagonal with portal spaces at
each cor 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 ture 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, a 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. Branch

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4 KLAASSEN AND WATKINS
are enclosed in a common vestment of connective tissue
and course through the portal space. Blood enters the 4

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 KLAASSEN AND V
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 t FROM THE CONSIDERT THE TREE ART AND THE CORRECT AND ARREST AND COURSE AND COURSE AND A point of the particle sinusoid from hepatic artery and portal vein, and flows centripetally through the lobule to exit via the central 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
 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 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, 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 por 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 r central veins and portal tracts cross at all angles, but the lobule is seen only when adjoining central and porta
veins are parallel and the tissue is sectioned at righ
angles to the axis of these vessels. However, the sim 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 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 aro angles to the axis of these vessels. However, the simpliver acinus was conceived as a microscopic parenchyma
mass of irregular shape and size that is arranged aroun
an axis formed by the portal triad (956, 957). The acin
a 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 landmass 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 land-
marks but extend outward to the terminal branches of
on an axis formed by the portal triad (956, 957). The acini
are not limited by any recognizable anatomical land-
marks but extend outward to the terminal branches of
one or more central veins. Interdigitation of terminal
bran are not limited by any recognizable anatomical land marks but extend outward to the terminal branches one or more central veins. Interdigitation of termine branches from three triangular portal spaces around o central venu marks 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, microscop one or more central veins. Interdigitation of terminal
branches from three triangular portal spaces around one
central venule creates a vascular pattern which, micro-
scopically, resembles a hexagon. The parenchyma is conules. ntral venule creates a vascular pattern which, micro-
opically, resembles a hexagon. The parenchyma is con-
uous between adjacent acini and between classic lob-
ss.
The sinusoids that separate the portal triad and central

scopically, 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 tinuous 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 ules.
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 ma-
trix of endothelial cells lacking complete basal 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 ma-
trix of endothelial cells lacking complete basal lamina 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 phagocy 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
occasion trix of endothelial cells lacking complete basal lamine and the branching pseudopodial Kupffer cell. The phagocytic cells normally lie on the luminal side boccasionally appear interposed between endothelial cell and form a 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. Inter-
cell phagocytic cells normally lie on the luminal side but
occasionally appear interposed between endothelial cells
and form a minor portion of the sinusoidal wall. Inter-
cellular gaps between endothelial cells, fenestrations, occasionally appear interposed between endothelial cells
and form a minor portion of the sinusoidal wall. Inter-
cellular gaps between endothelial cells, fenestrations, and
lack of complete basal lamina permit blood plasma and form a minor portion of the sinusoidal wall. Inte cellular gaps between endothelial cells, fenestrations, an lack of complete basal lamina permit blood plasma containing endogenous and exogenous substances to enture th cellular gaps between endothelial cells, fenestrations, and
lack of complete basal lamina permit blood plasma con-
taining endogenous and exogenous substances to enter
the space of Disse (fig. 2), i.e. between sinusoidal m 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 m 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 norma e space of Disse (fig. 2), i.e. between sinusoidal mem-
ane and hepatocytes, and to have direct contact with
e microvilli of the parenchymal cell membrane. Red
ood cells cannot pass into the space of Disse.
The normal youn brane and hepatocytes, and to have direct contact we the microvilli of the parenchymal cell membrane. Reflood cells cannot pass into the space of Disse.
The normal young adult rat has two main cell typeratic parenchymal ce

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. Paren-
chymal cells 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. Paren-
chymal cells constitute 90% to 95% of total liver weight
but only The normal young adult rat has two main cell types,
hepatic parenchymal cells and endothelial cells. Paren-
chymal cells constitute 90% to 95% of total liver weight
but only 60% to 65% of total cell population chymal 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 40% of total cellular population (727). Phagocytic Kupfbut 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 Ku 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 Kupf-
fer cells remove and digest organisms and partic 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 b 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) ar fer 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
po 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 pos-
 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 arran 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 arran 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 membrane. ment 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 di

ment 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 di 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 dis-
tance from the vessels supplying blood (fig. 3). C membrane.
Whether using the classic lobule or the liver acinus
concept, hepatocytes can be separated based upon dis-
tance from the vessels supplying blood (fig. 3). Cells in
zone 1, or periportal region, are near the port

lamina.

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

REVIEW

PHARMACOLOGICAL

than to portal venous blood. Cells in zone 3, or centrilob-BILE FORMATION, HEPATION
and are bathed by blood closer in composition to arte
than to portal venous blood. Cells in zone 3, or centri
ular region, are in a zone in which no arteriole en BILE FORMATION, HEPATIC UPTA
and are bathed by blood closer in composition to arterial
than to portal venous blood. Cells in zone 3, or centrilob-
ular region, are in a zone in which no arteriole enters
and are situated at and are bathed by blood closer in composition to arterial (d
than to portal venous blood. Cells in zone 3, or centrilob-
ular region, are in a zone in which no arteriole enters and
and are situated at the microcirculatory and are bathed by blood closer in composition to arterial (conduction 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 pe 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 ular region, are in a zone in which no arteriole enters and
and are situated at the microcirculatory periphery around (56
the central vein. Zone 2, or midzonal region, is a dividing 2.5
layer of tissue between zones 1 and and are situated at the microcirculatory periphery arous
the central vein. Zone 2, or midzonal region, is a dividi
layer of tissue between zones 1 and 3. Heterogenei
between centrilobular and periportal cells has bee
shown 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). Hepa-
to layer of tissue between zones 1 and 3. Heterogene
between centrilobular and periportal cells has be
shown by histochemical studies (572, 859, 1223). He
tocytes may be fractionated by centrifugation on Fid
density gradients between centrilobular and periportal cells has b
shown by histochemical studies (572, 859, 1223). He
tocytes may be fractionated by centrifugation on Fi
density gradients (166) into two classes: 1) light hep
cytes (mean de tocytes may be fractionated by centrifugation on Ficoll
density gradients (166) into two classes: 1) light hepato-
cytes (mean density 1.10) are predominantly centrilob-
ular and contain abundant smooth endoplasmic reticutocytes may be fractionated by centrifugation on Ficoll Sidensity gradients (166) into two classes: 1) light hepato-
cytes (mean density 1.10) are predominantly centrilob-
ular and contain abundant smooth endoplasmic retic density gradients (166) into two classes: 1) light hepatocytes (mean density 1.10) are predominantly centrilob-
ular and contain abundant smooth endoplasmic reticu-
lum, numerous small mitochondria, and few glycogen
granul cytes (mean density 1.10) are predominantly centrilob-
ular and contain abundant smooth endoplasmic reticu-
lum, numerous small mitochondria, and few glycogen
granules; and 2) heavy hepatocytes (mean density 1.14)
are prim ular and contain abundant smooth endoplasmic reticum, numerous small mitochondria, and few glycogen granules; and 2) heavy hepatocytes (mean density 1.1-
are primarily periportal and are characterized by larg
compact glyco 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 granules; and 2) heavy hepatocytes (mean density 1.14) p
are primarily periportal and are characterized by large,
compact glycogen granules and prominent rough endo-
plasmic reticulum (266, 441, 442, 1231). Centrilobula are primarily periportal and are characterized by large,
compact glycogen granules and prominent rough endo-
plasmic reticulum (266, 441, 442, 1231). Centrilobular
cells contain larger amounts of lysosomes and smooth
endop compact glycogen granules and prominent rough endo-
plasmic reticulum (266, 441, 442, 1231). Centrilobular
cells contain larger amounts of lysosomes and smooth
in endoplasmic reticulum than periportal hepatocytes (565,
al plasmic 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 th cells contain larger amounts of lysosomes and smooth
endoplasmic reticulum than periportal hepatocytes (565, all c
754). In addition, bile canaliculi are larger in zone 1 than
in zone 3 while those in zone 3 dilate more i 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 canalicul in zone 3 while those in zone 3 dilate more in respone to bile acid-induced choleresis than canaliculi in zone (719). Within the acinus, differences exist in oxygentension, in rates of enzymes mediating protein synthesion in zone 3 while those in zone 3 dilate more in resp
to bile acid-induced choleresis than canaliculi in zo
 (719) . Within the acinus, differences exist in oxy
tension, in rates of enzymes mediating protein synth
oxidation 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 concen (719). Within the acinus, differences exist in oxygen
tension, in rates of enzymes mediating protein synthesis,
oxidation, hydrolysis and conjugation, and in concentra-
tion of glutathione (444, 1156). However, this funct tension, in rates of enzymes mediating protein synthesis,
oxidation, hydrolysis and conjugation, and in concentra-
tion of glutathione (444, 1156). However, this functional
heterogeneity does not result from differential e oxidation, hydrolysis and conjugation, and in concentra-
tion of glutathione (444, 1156). However, this functional con-
heterogeneity does not result from differential expression $\frac{3\%}{100}$
of genetic properties inhere

of genetic properties inherent in hepatocytes but rather
reflects quantitative differences in functional require-
ments.
There is a lobular gradient in the sinusoids as cells on
the periphery of the lobule (zone 1 or peri reflects quantitative differences in functional requires.

There is a lobular gradient in the sinusoids as cell

the periphery of the lobule (zone 1 or periportal)

perfused first with blood containing higher concer

tions ments.

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 concentra-

tions of solutes while cells near the termi 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 concentra-
tions of solutes while cells near the terminal hepatic the periphery of the lobule (zone 1 or periportal)
perfused first with blood containing higher concentions of solutes while cells near the terminal hep-
veins (central vein, zone 3) are perfused last and expo-
to blood wit perfused first with blood containing higher concentra-
tions 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 unidi tions of solutes while cells near the terminal hepatories (central vein, zone 3) are perfused last and expose to blood with less solute. However, flow is not uniditional because of the nonuniformity of resistances with the veins (central vein, zone 3) are perfused last and expose
to blood with less solute. However, flow is not unidire
tional because of the nonuniformity of resistances withi
the hepatocyte syncytium and the intermittent anast to blood with less solute. However, flow is not unidiversional because of the nonuniformity of resistances with the hepatocyte syncytium and the intermittent anas moses of hepatic arterioles into zones 2 and 3. Co pounds t tional because of the nonuniformity of resistances within
the hepatocyte syncytium and the intermittent anasto-
moses of hepatic arterioles into zones 2 and 3. Com-
pounds that diffuse through membranes will be concen-
tra 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 moses 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 pounds 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 nonuni trated in periportal cells, while solutes requiring a carrier will behave differently depending on the availability of of transport systems. This lobular gradient of nonuniform spectrosure of liver cells to solutes has bee 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) . Example 1 and space of liver cells to solute a has been illustrated for posure of liver cells to solutes has been illustrated for the lactose (402) , fluorescent dyes (445) , and a bile acid rivative (563) .
In additio

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 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 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 μ m which are
climited by, and located between, In addition to the labyrinthine sinusoids, the biliar system branches throughout the liver. Bile canaliculi a extracellular spaces as minute as 1 to 2 μ m which a limited by, and located between, two or more abuttinepat system branches throughout the liver. Bile canaliculi is extracellular spaces as minute as 1 to 2 μ m which is limited by, and located between, two or more abuttifulned by tight junctions that are stabilized by desmomes limited by, and located between, two or more abutting
hepatocytes. The integrity of the biliary space is main-
tained by tight junctions that are stabilized by desmo-
somes and microfilaments (104, 375, 500, 862). Generall limited by, and located between, two or more abutting ess
hepatocytes. The integrity of the biliary space is main-
tained by tight junctions that are stabilized by desmo-
becomes and microfilaments $(104, 375, 500, 862)$. hepatocytes. The integrity of the biliary space is main-
tained by tight junctions that are stabilized by desmo-
somes and microfilaments (104, 375, 500, 862). Generally,
a single canaliculus courses between adjacent cells tained by tight junctions that are stabilized by desmo-
somes and microfilaments $(104, 375, 500, 862)$. Generally, is
a single canaliculus courses between adjacent cells and p
forms a tridimensional network of channels t

BILE FORMATION, HEPATIC UPTAKE, AND BILIARY EXCRETION 5
and are bathed by blood closer in composition to arterial (ducts of Hering, or cholangioles) lined with cuboidal epithelium. The functional properties of bile ductules AKE, AND BILIARY EXCRETION 5
(ducts of Hering, or cholangioles) lined with cuboidal
epithelium. The functional properties of bile ductules
and ducts in bile secretion have not been determined 4 ME, AND BILIARY EXCRETION 5
(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 (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
 (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
 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
 $2.5 \ \mu l/g$ of liver (75) and in rats, 2.3 (65, 452). Th (566). The apparent volume of the biliary tree in dogs is 2.5 μ l/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 t (566). The apparent volume of the biliary tree in dogs is $2.5 \mu l/g$ 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 2.5μ /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 duodenu duct from each lobe intersects forming the l
which anastomoses with the pancreatic duct
common bile duct which empties into the
Some species (rat, whale, and deer) do not
bladder that branches off the hepatic duct.
III Bil **III.** Which empties into the particular of the set of the hepatic duct
III. Bile Composition
of bile varies among species

me species (rat, whale, and deer) do not have a gall-

adder that branches off the hepatic duct.

III. Bile Composition

Composition of bile varies among species and upon the

ysiological and nutritional status of the anim bladder 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 indicat 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 sev **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 an** 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 concentration of biliary constituents in several species. Bile and 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 of biliary constituents in several species. Bile and plasma
have similar electrolyte compositions; sodium is the dom-
inant cation, while bile acids, chloride, and bicarbonate
all contribute to total anion content. In addi of biliary constituents in several species. Bile and plass
have similar electrolyte compositions; sodium is the do
inant cation, while bile acids, chloride, and bicarboni
all contribute to total anion content. In addition, have similar electrolyte compositions; sodium is the cinant cation, while bile acids, chloride, and bicarboall contribute to total anion content. In addition, contains significant amounts of bile pigments, characterol, pho all contribute to total anion content. In addition, bile contains significant amounts of bile pigments, choles-
terol, phospholipids, and protein. Relative concentra-
tions of organic solutes and inorganic electrolytes may contains significant amounts of bile pigments, choles-
terol, phospholipids, and protein. Relative concentra-
tions of organic solutes and inorganic electrolytes may
fluctuate but the osmolarity of bile is generally equiva terol, phospholipids, and protein. Relative concentra-
tions 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 a tions 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 arti-
ficially increased or decreased (1245). Average wa fluctuate but the osmolarity of bile is generally equivalent
to that of plasma even when plasma osmolarity is arti-
ficially increased or decreased (1245). Average water
content of bile is approximately 97%. Almost half of to that of plasma even when plasma osmolarity is arti-
ficially 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, wa ficially increased or decreased
content of bile is approximately !
3% solid material is bile acids. In
content is lower (87%) which res
of hepatic bile by the gallbladder
Marked species differences ntent of bile is approximately 97%. Almost half of the
6 solid material is bile acids. In gallbladder bile, water
ntent is lower (87%) which results from concentration
hepatic bile by the gallbladder.
Marked species differ

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 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 b 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. T 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 d 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 di 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 wit conjugating group. These variations correlate roughly
with diet; herbivores, except bovids, have primarily di-
hydroxy or monohydroxymonoketo bile acids conjugated
with glycine, whereas carnivores have taurine conjugates
o with diet; herbivores, except bovids, have primarily di-
hydroxy or monohydroxymonoketo bile acids conjugated
with glycine, whereas carnivores have taurine conjugates
of trihydroxy bile acids. Omnivores and bovids have
sig hydroxy 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
domes with glycine, whereas carnivores have taurine conjugat
of trihydroxy bile acids. Omnivores and bovids ha
significant amounts of all types (470). The rabbit at
domestic pig excrete bile acids conjugated with glyci
while hum 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 conju-
gate 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 domestic pig excrete bile acids conjugated with glycine
while humans eliminate both glycine and taurine conju-
gates of dihydroxy and trihydroxy bile acids. This dietary
classification has exceptions such as the high propo while humans eliminate both glycine and taurine con gates of dihydroxy and trihydroxy bile acids. This dietally classification has exceptions such as the high proportion f taurocholate in rat bile (207, 469, 1244). Mark sp gates of dihydroxy
classification has e
of taurocholate in
species variations
terol concentration **IV.** Bile Formation
IV. Bile Formation
IV. Bile Formation
ile by hepatocytes is a ma ecies variations occur also in phospholipid and choles-
rol concentrations.
IV. Bile Formation
Production of bile by hepatocytes is a major, but poorly
derstood function of the liver. Bile formed at the

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 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 w 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 be 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 difficul because the primary secretion elaborated by hepatocyte i esses of reabsorption or secretion of electrolytes and water. The study of hepatic bile formation is difficul because the primary secretion elaborated by hepatocyte is discharged into minute channels and cannot be sam pled water. The study of hepatic bile formation is difficult
because the primary secretion elaborated by hepatocytes
is discharged into minute channels and cannot be sam-
pled directly with current micropuncture techniques
Tran because the primary secretion elaborated by hepatocyte
is discharged into minute channels and cannot be sam
pled directly with current micropuncture techniques
Transmembrane ion fluxes and electrical potentials can
not be

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* Klaassen (632).

Example 18 (216).
 Figh and Stone (951).
 f Thureborn (1178).
 § Cornelius (216).
 Russell et al. (1015).

much research has been conducted in recent years. Com-
g Cornelius (216).
much research has been conducted in recent years. Com-
prehensive reviews pertaining to mechanisms of bill **prefixed** Formelius (216).
 Prehensive reviews pertaining to mechanisms of bile
 prehensive reviews pertaining to mechanisms of bile uliformation are available and may be consulted for details do **Formation are available and may be consulted in recent years.** Comprehensive reviews pertaining to mechanisms of bile formation are available and may be consulted for details of earlier work $(124, 305-307, 309, 354, 556$ 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, much resear
prehensive
formation a
of earlier w
887, 970).
A Osmotic **France Standard Schools**
A. Osmotic Ultrafiltration
A. Osmotic Ultrafiltration
The central problem to 1 earlier work $(124, 305-307, 309, 354, 556, 566, 570,$ po

7, 970).

Osmotic Ultrafiltration muderstanding canalicular bile

The central problem to understanding canalicular bile

this mation is comprehension of the mecha

Formation is comprehension of the mechanisms general problem to understanding canalicular bornation is comprehension of the mechanisms generating bulk movement of water into bile canaliculi. Portion, the mechanisms are ext A. Osmotic Ultrafiltration
The central problem to understanding canalicular bile
formation is comprehension of the mechanisms gener-
ating bulk movement of water into bile canaliculi. Pos-
sibilities include filtration, ve A. *Usmotic Ultrajultration*
The central problem to understanding canalicular bile
formation is comprehension of the mechanisms gener-
ating bulk movement of water into bile canaliculi. Pos-
sibilities include filtration, The central problem to understanding canalicular bile
formation is comprehension of the mechanisms gener-
ating bulk movement of water into bile canaliculi. Pos-
sibilities include filtration, vesicular transport, and ac-
 flow. Ing bulk movement of water into bile canaliculi. Positities include filtration, vesicular transport, and ac-
re transport of certain solutes leading to passive water
w.
In contrast to the kidney, the architecture of the l

sibilities 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 tive 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 pre flow.
In contrast to the kidney, the architecture of the liver
does not provide an efficient arrangement for hydrostatic $\frac{3}{16}$
filtration. Bile is secreted against a pressure gradient
that exceeds perfusion pressure In contrast to the kidney, the architecture of the liver
does not provide an efficient arrangement for hydrostatic $\frac{1}{3}$
filtration. Bile is secreted against a pressure gradient
that exceeds perfusion pressure in the filtration. Bile is secreted against a pressure gradient latex exceeds perfusion pressure in the isolated perfused rat liver (135). In addition, bile flow is independent of aperfusion pressure and blood flow once a critic that exceeds perfusion pressure in the isolated perfus
rat liver (135). In addition, bile flow is independent
perfusion pressure and blood flow once a critical openi
pressure is obtained and the oxygen supply to the tiss
i rat liver (135). In addition, bile flow is independent of an perfusion pressure and blood flow once a critical opening dupressure is obtained and the oxygen supply to the tissue miss not limited (136, 137). These results production. Example is obtained and the oxygen supply to the tissue
not limited (136, 137). These results rule out hydro-
ritic pressure as an important determinant for bile
isoduction.
Another mechanism that may be operative in bile

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. static 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, production.

Another mechanism that may be operative in bile

formation is the extrusion of materials by exocytosis.

Horseradish peroxidase (978), lysosomal proteins (710, value 1711), immunoglobulin A (725), and insulin Another mechanism that may be operative in bile
formation is the extrusion of materials by exocytosis. a
Horseradish peroxidase (978), lysosomal proteins (710, v
711), immunoglobulin A (725), and insulin (228) are b
thoug 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 Horseradish peroxidase (978), lysosomal proteins (7
711), immunoglobulin A (725), and insulin (228) a
thought to be secreted into bile by a pathway involvi
the Golgi, associated lysosomes, and smooth endoplase
reticulum (5 711), 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 de thought to be secreted into bile by a pathway involving
the Golgi, associated lysosomes, and smooth endoplasmic
reticulum (566). Although vesicular transport is demon-
strated by the above examples, infrequent visualizati the Golgi, associated lysosomes, and smooth endopla
reticulum (566). Although vesicular transport is der
strated by the above examples, infrequent visualize
of exocytic vacuoles suggests this excretory step does
contribute reticulum (566)
strated by the
of exocytic vacu
contribute sign
lar bile (354).
Present conc rated by the above examples, infrequent visualization B .
exocytic vacuoles suggests this excretory step does not
ntribute significantly to the formation of hepatocellu-
vicible (354).
Present concepts of bile formation

of exocytic vacuoles suggests this excretory step does not contribute significantly to the formation of hepatocellu-
lar bile (354).
Present concepts of bile formation evolved from the
initial hypothesis of Sperber (1114) contribute significantly to the formation of hepatocellu-
lar bile (354).
Present concepts of bile formation evolved from the
initial hypothesis of Sperber (1114) that any osmotically
hunder compound transported into bile lar 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 int Present concepts of bile formation evolved from the hinitial hypothesis of Sperber (1114) that any osmotically hactive compound transported into bile can create an (10) osmotic gradient from the hepatocyte into the canalic 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

continue to flow if solute is transported into the canal
uli, providing that resistance to flow in the biliary t continue to flow if solute is transported into the canalic-
uli, providing that resistance to flow in the biliary tree
does not exceed the osmotic pressure created by transcontinue to flow if solute is transported into the canali
uli, providing that resistance to flow in the biliary tr
does not exceed the osmotic pressure created by tran
ported solute(s). continue to flow
uli, providing th
does not exceed
ported solute(s).
Canalicular bi ntinue to flow if solute is transported into the canalic-
i, providing that resistance to flow in the biliary tree
es not exceed the osmotic pressure created by trans-
rted solute(s).
Canalicular bile formation is estimate

In contrast to the kidney, the architecture of the liver
the rate of bile flow at a specified locus (350, 351, 353,
does not provide an efficient arrangement for hydrostatic 356 , 1245). Clearances of erythritol and mann uli, providing that resistance to flow in the biliary tree
does not exceed the osmotic pressure created by trans-
ported solute(s).
Canalicular bile formation is estimated indirectly by
measuring the biliary clearance of i 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 modif ported solute(s).
Canalicular bile formation is estimated indirectly b
measuring the biliary clearance of inert solutes, who
elimination is not significantly modified by processes i
bile ductules and ducts, that enter the 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 ca elimination is not significantly modified by processes in
bile ductules and ducts, that enter the bile at the cana-
liculi by simple, nonrestricted diffusion. The solutes,
erythritol and mannitol, have been thought to meet continue to flow if solute is transported into the canalic-
uli, providing that resistance to flow in the biliary tree
does not exceed the osmotic pressure created by trans-
ported solute(s).
Canalicular bile formation is bile ductules and ducts, that enter the bile at the can
liculi by simple, nonrestricted diffusion. The solute
erythritol and mannitol, have been thought to meet the
requirements. Hepatocytes are remarkably permeable
erythr liculi 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 excr erythritol and mannitol, have been thought to meet these
requirements. Hepatocytes are remarkably permeable to
erythritol and mannitol (353, 392, 897), and their excre-
tion depends on the permeability of the epithelium an requirements. Hepatocytes are remarkably permeable erythritol and mannitol (353, 392, 897), and their excrtion depends on the permeability of the epithelium are the rate of bile flow at a specified locus (350, 351, 35
356, 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 co 356, 1245). Clearances of erythritol and mannitol correthe 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 d 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 late with changes in bile flow during bile acid-induc
canalicular choleresis. However, recent studies in do
and rhesus monkeys suggest that secretin, which induc
ductular bile production, also stimulates erythritol an
mann 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 ery and rhesus monkeys suggest that secretin, which induce
ductular bile production, also stimulates erythritol an
mannitol clearance (61, 74, 737). The transfer of eryth
ritol, sucrose, and inulin from plasma to bile acros
is ductular bile production, also stimulates erythritol and
mannitol clearance (61, 74, 737). The transfer of eryth-
ritol, sucrose, and inulin from plasma to bile across
isolated perfused duct segments from rats is proportio ritol, 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
af magnitude of canalicular bile formation may also be 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 t 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 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), it affected if back diffusion of solutes occurs.

validity of erythritol as a measurement o

bile production has been questioned (256, 7

clearance provides the only quantitative est

alicular bile production presently availa *B. Bile production has been questioned*
 B. Bile Acid-dependent Flow
 B. Bile Acid-dependent Flow

In 1890. Schiff demonstrated tha France provides the only quantitative estimate of cancular bile production presently available.

Bile Acid-dependent Flow

In 1890, Schiff demonstrated that feeding bile to dogs

th biliary fistulas produced a choleresis.

metricular bile production presently available.

A. 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 bil R. 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 obser B. Bue Acud-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 observ 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, inc 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 mos 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 th 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 th 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

PHARMACOLOGICAL REVIEWS

BILE FORMATION, HEPATIC UPTAKE, AND BILIARY EXCRETION
pony (37) indicate that bile flow rate is directly propor-
tional to the rate of sodium taurocholate excretion after
intravenous infusion over a wide concentration rang tional to the rate of sodium taurocholate excretion after BILE FORMATION, HEPATIC UP
pony (37) indicate that bile flow rate is directly propor-
tional to the rate of sodium taurocholate excretion after
intravenous infusion over a wide concentration range.
Normally, bile acids are

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 mic tional to the rate of sodium taurocholate excretion after
intravenous infusion over a wide concentration range.
Normally, bile acids are present in bile as mixed mi-
celles (161), and their osmotic activity in bile is gene 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. Dehydrochol 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 celles (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 less than that of nonassociated molecules. Dehydrocholacid does not form micelles and produces choleresis at lower concentration than does micelle-forming choliacid (1116). Although a single micelle has a similar osmotic a 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 effec 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 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 osmotic activity as
tive osmotic pressu
large polyanionic a
about 27,000 (556)
bile acid molecules.
However, canalic re osmotic pressure is greatly reduced by formation of ge polyanionic aggregates with a molecular weight of out 27,000 (556). Each micelle contains around 500 e acid molecules.
However, canalicular bile is not produced com

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 acid 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 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 eff 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).
C by the osmotic properties of bile acids. Interruption
the enterohepatic circulation markedly decreases bi
acid excretion but has little effect on bile flow (625
Conflicting data for dehydrocholate-induced choleres
indicate 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 exc acid excretion but has little effect on bile flow (623)
Conflicting data for dehydrocholate-induced choleresi
indicate that the increase in bile flow precedes the excretion of dehydrocholate by more than can be accounte
fo tion of dehydrocholate by more than can be accounted tion 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 ta for by the biliary tree dead space (1109). Bile flow asso-
ciated with secretion of micelle-forming cholate may
actually exceed that associated with non-micelle-forming
taurodehydrocholate (875). Attempts to correlate cho ciated with secretion of micelle-forming cholate may $^{(3)}$ actually exceed that associated with non-micelle-forming is
taurodehydrocholate (875). Attempts to correlate chollaretic properties with micelle-forming capaciti actually exceed that associated with non-micelle-forming
taurodehydrocholate (875). Attempts to correlate chol-
eretic properties with micelle-forming capacities of bile
acids in vitro have failed (37, 630, 876, 1067). The taurodehydrocholate (875). Attempts to correlate cheretic properties with micelle-forming capacities of b
acids in vitro have failed (37, 630, 876, 1067). The b
acid-dependent fraction has also been proposed to res
from os eretic 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 a 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 accom-
pany anionic bile acids to maintain electrical neut acid-dependent fraction has also been proposed to result
from osmotic activity of inorganic cations that accom-
pany anionic bile acids to maintain electrical neutrality.
The osmotic activity of a solute depends on the rel from osmotic activity of inorganic cations that accom-
pany 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 permeability of the membrane to solute as compared to permeability of the membrane to solute as compared to solvent, or its reflection coefficient (566). Reflection $\frac{\ln 3}{10}$ coefficients of the biliary tree for different solutes are incurknown due to the technological in solvent, or its reflection coefficient (566) . Reflection $\frac{ln \epsilon}{c}$ coefficients of the biliary tree for different solutes are inclunknown due to the technological inability to sample stin bile at the canaliculus. Bile coefficients of the binary 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 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

believed to be due to the osmotic activity of bile acids, C. Bile Acid-independent Flow of the may be although hepatocellular bile formation was originally cretion believed to be due to the osmotic activity of bile acids, separalinear extrapolation of the regression line for bile C. Bue Acud-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 excreti Although hepatocellular bile formation was originally collective of bile acids, slinear extrapolation of the regression line for bile flow nuclear extrapolation of the regression line for bile flow nuclear secretion in the believed to be due to the osmotic activity of bile alinear extrapolation of the regression line for bile versus bile acid excretion to the ordinate indicates alicular secretion in the absence of bile acid excree (fig. 4) (linear extrapolation of the regression line for bile flow mor
versus bile acid excretion to the ordinate indicates can-
alicular secretion in the absence of bile acid excretion dog
(fig. 4) (1254). This bile is termed the versus bile acid excretion to the ordinate indicates can-
alicular secretion in the absence of bile acid excretion
(fig. 4) (1254). This bile is termed the bile acid-inde-
pendent fraction and has been observed repeatedly (fig. 4) (1254). This bile is termed the bile acid-inde-
pendent fraction and has been observed repeatedly in cA
many species including dogs, rats, rabbits, and humans do
 $(102, 125, 251, 311, 938, 958, 1148, 1254)$. In c pendent 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
inde many species including dogs, rats, rabbits, and humans d
(102, 125, 251, 311, 938, 958, 1148, 1254). In contrast, a
chickens produce only small amounts of bile that are b
independent of bile acid secretion (157). However, (102, 125, 251, 311, 938, 958, 1148, 1254). In contrast, action
chickens produce only small amounts of bile that are bile
independent of bile acid secretion (157). However, rep-
resentation of the bile flow versus bile ac independent of bile acid secretion (157). However, rep-
resentation of the bile flow versus bile acid excretion
relationship by a single regression line may not be valid a
since infusion of bile acids into bile acid-deplet resentation of the bile how versus bile acid excretion can
relationship by a single regression line may not be valid al.
since infusion of bile acids into bile acid-depleted rats or
rhesus monkeys results in a family of re

indicate that the increase in bile flow precedes the excre-
tion of dehydrocholate by more than can be accounted concentrations (< 10 mM), the slope of the regression
for by the biliary tree dead space (1109). Bile flow a **BILE ACID EXCRETION**
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 **EILE ACID EXCRETION**
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 approxi FIG. 4. Linear extrapolation of bile flow versus bile acid excretion.
acid concentration increases (52, 58). At low bile acid
concentrations ($\lt 10$ mM), the slope of the regression
line is approximately 10 times that fo acid concentration increases $(52, 58)$. At low bile acid concentrations $(< 10 \text{ mM})$, the slope of the regression line is approximately 10 times that found at higher levels $(35 \text{ to } 45 \text{ mM})$. Thus, the osmotic activity o acid concentration increases (52, 55). 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 line is approximately 10 times that found at higher leve $(35 \text{ to } 45 \text{ mM})$. Thus, the osmotic activity of bile acides is relatively greater at lower concentrations, and calcelation of the bile acid-independent fraction o 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 secre-
tion at concentrations above 10 mM might overes lation 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)

The osmotic activity of a solute depends on the relative of spontaneous basal bile secretion in humans (742) and
permeability of the membrane to solute as compared to about 60% in lagomorphs and rodents (311, 623, 1080 The bile acid-independent fraction of canalicular bile tion 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 hum 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, 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 $(311, 62$ 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
i 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 day increases bile formation by 50% in the rat but about $60%$ in lagomorphs and rodents (311, 625, 1060).
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 increases bile formation by 50% in the rat but does not stimulate bile acid excretion (102, 622, 623). Other studsecretory pressures even with negligible bile acid secre-

transport systems for other osmotically active solutes tion (127).

such as sodium ion (632, 928, 1230).

C. Bile Acid-independent Flow

C. Bile Acid-independent Flow

Although hepatocellular bile formation was originally independent of bile acid secretion (157). However, rep-
resentation of the bile flow versus bile acid excretion cAMP do not stimulate bile flow (51). In fact, Poupon et
relationship by a single regression line may not be v *1. Sodium Ion Secretion.* The mechanism for formation may be due to sodium, chloride, or bicarbonate ion exion (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 ex-

cretion. Sodium ion secretion has been impl 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 ex-
cretion. Sodium ion secretion has been implicated by two
se of the bile acid-independent fraction is not known but
may be due to sodium, chloride, or bicarbonate ion ex-
cretion. Sodium ion secretion has been implicated by two
separate lines of evidence. First, cyclic 3',5'-adenosi may be due to sodium, chloride, or bicarbonate ion ex-
cretion. Sodium ion secretion has been implicated by two
separate lines of evidence. First, cyclic 3',5'-adenosine
monophosphate (cAMP) increases sodium ion transport
 cretion. 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
 monophosphate (cAMP) increases sodium ion transport
out of the hepatocytes and stimulates bile flow in the
dog by increasing bile acid-independent flow (885). Glu-
cagon and theophylline, which increase intracellular
cAMP monophosphate (cAMP) increases sodium ion transport
out of the hepatocytes and stimulates bile flow in the
dog by increasing bile acid-independent flow (885). Glu-
cagon and theophylline, which increase intracellular
cAMP out of the hepatocytes and stimulates bile flow in the dog by increasing bile acid-independent flow (885). Glu-
cagon and theophylline, which increase intracellular
cAMP levels, also stimulate this fraction of bile flow in dog by increasing bile acid-independent flow (885). Glu-
cagon and theophylline, which increase intracellular
cAMP levels, also stimulate this fraction of bile flow in
dogs (70, 567). In addition, theophylline increases bi cAMP levels, also stimulate this fraction of bile flow
dogs (70, 567). In addition, theophylline increases
acid-independent flow in rats but does not increase
bile flow because the bile acid-dependent fraction
decreased (6 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-
cA acid-independent flow in rats but does not increase need 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 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, ami-
nop decreased (674). In the rat, glucagon and dibutyrylthe accumulation of cAMP or 2) the magnitude of the

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REAASSEN
The in camp, and the increase in bile flow. They con-
cluded cAMP does not have a physiological role in bile KLAASSEN AND

rise in cAMP, and the increase in bile flow. They con-

cluded cAMP does not have a physiological role in bile

formation. Whether other cyclic nucleotides, such as bra KLAASSEN AND
rise in cAMP, and the increase in bile flow. They con-
cluded cAMP does not have a physiological role in bile
formation. Whether other cyclic nucleotides, such as br
cyclic guanosine monophosphate, are cellula 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 sec 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 sec cluded cAMP does not have a physiological role in bile pl
formation. Whether other cyclic nucleotides, such as bi
cyclic guanosine monophosphate, are cellular mediators list
of secretion is unknown, but reductions in extra ration. Whether other tythe interestinces, such as brack-
cyclic guanosine monophosphate, are cellular mediators line
of secretion is unknown, but reductions in extracellular Ph
calcium ion markedly inhibit bile production excluded. 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 excret

rat liver (665). I hus, an interferationship between cyclic
nucleotides, calcium fluxes and bile secretion cannot be
excluded.
Second, modulation of sodium ion excretion by con-
trolling Na⁺-K⁺-adenosine triphosphatase mucreotides, carcium riaxes and one secretion cannot be planet
excluded.
trolling Na⁺-K⁺-adenosine triphosphatase (ATPase) ac-
tivity is thought to influence the formation of this frac-
tion of bile flow. Na⁺-K⁺-AT 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. $Na^-.K^-.ATP$ ase was implicated when inhibito trolling $Na^+ \cdot K^+$ -adenosine triphosphatase (ATPase) actrivity is thought to influence the formation of this fraction of bile flow. $Na^+ \cdot K^+$ -ATPase was implicated when sodiphibitors such as amiloride, ethacrynic acid, tivity is thought to influence the formation of this fraction of bile flow. Na⁺-K⁺-ATPase was implicated when simbibitors such as amiloride, ethacrynic acid, and oua-
bain diminished the bile acid-independent fraction tion of bile flow. $Na^+ \cdot K^+ \cdot ATP$ as was implicated when similarity in action as a amiloride, ethacrynic acid, and oua-
bain diminished the bile acid-independent fraction in rabbits (310, 311). In contrast, later studies inhibitors such as amiloride, ethacrynic acid, and oua-
bain diminished the bile acid-independent fraction in
rabbits (310, 311). In contrast, later studies indicated the
chacrynic acid produces choleresis in rabbits and r bain diminished the bile acid-independent fraction in marabbits (310, 311). In contrast, later studies indicated the ethacrynic acid produces choleresis in rabbits and rats act (178, 658, 1078), and ouabain increases bile 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 tha 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 perfuse (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 (410, 1017). Graf and Peterlik (412) suggested that the scholeretic effect of ouabain in the isolated perfused rat (iver results from inhibition of sinusoidal Na⁺-K⁺-ATPase. The consequential rise in intracellular Na choleretic effect of ouabain in the isolated perfused
liver results from inhibition of sinusoidal Na⁺-H
ATPase. The consequential rise in intracellular N
concentration would stimulate the canalicular ATP;
to extrude more liver results from inhibition of sinusoidal Na⁺-K⁺-2
ATPase. The consequential rise in intracellular Na⁺ of a
concentration would stimulate the canalicular ATPase of
to extrude more sodium ion thereby increasing can 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 ithe concentration would stimulate the canalicular ATPs
to extrude more sodium ion thereby increasing canal
ular bile flow. However, unaltered ouabain (1017) at
the glutathione conjugate of ethacrynic acid (178, 65
are readily to extrude more sodium ion thereby increasing canalic
ular bile flow. However, unaltered ouabain (1017) and
the glutathione conjugate of ethacrynic acid (178, 658
are readily concentrated in bile, and choleresis is attrib
 ular bile flow. However, unaltered ouabain (1017) and
the glutathione conjugate of ethacrynic acid (178, 658)
are readily concentrated in bile, and choleresis is attrib-
utable to an osmotic effect of the drugs themselves. 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 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 conj utable to an osmotic effect of the drugs themselves. de
Recent evidence suggests both mechanisms may be im-
portant in that canalicular excretion of the glutathione
conjugate is rate-limiting but is accompanied by en-
han portant in that canalicular excretion of the glutathione traconjugate is rate-limiting but is accompanied by enhanced extrusion of Na⁺ into the canalicular lumen so (908). Others indicate that vasoconstrictive actions of conjugate is rate-limiting but is accomplanced extrusion of Na⁺ into the cana
(908). Others indicate that vasoconstrict
cardiac glycosides might account for the re
acid-independent flow (812, 1162, 1177).
The affect of n nced extrusion of Na^+ into the canalicular lumen
08). Others indicate that vasoconstrictive actions of
rdiac glycosides might account for the reduction in bile
id-independent flow (812, 1162, 1177).
The affect of numero

(908). Others indicate that vasoconstrictive actions cardiac glycosides might account for the reduction in bilection in bilection in the affect of numerous compounds on bile formation (rose bengal (704) , ethinylestradio 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), acid-independent flow (812, 1162, 1177).
The affect of numerous compounds on bile formati
[rose bengal (704), ethinylestradiol (968), phenobarbi
(968, 1091), taurocholate (1230), thyroid hormones (71
ethanol (762), and cyc The affect of numerous compounds on bile formation
[rose bengal (704), ethinylestradiol (968), phenobarbita
(968, 1091), taurocholate (1230), thyroid hormones (717)
ethanol (762), and cycloheximide (747)] has been attrib
 [rose bengal (704), ethinylestradiol (968), phenobarbi
(968, 1091), taurocholate (1230), thyroid hormones (71
ethanol (762), and cycloheximide (747)] has been attr
uted to influences on Na⁺-K⁺-ATPase supposedly pr
ent (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 demon 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 latera uted 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). Alterati strates that $Na^+ \cdot K^+ \cdot ATP$ ase is located on the sinusoidal
and lateral surfaces of the hepatocytes (113, 715, 934).
Alterations in bile acid-independent flow and $Na^+ \cdot K^+$ -
ATP ase activity do not always change in para strates that Na⁺-K⁺-ATPase is located on the sinusoidal app
and lateral surfaces of the hepatocytes (113, 715, 934). have
Alterations in bile acid-independent flow and Na⁺-K⁺-846
ATPase activity do not always chan and lateral surfaces of the hepatocytes (113, 715, 934). ha
Alterations in bile acid-independent flow and $Na^{+} - K^{+}$ 84
ATPase activity do not always change in parallel (595, C
796). Thus, generation of this fraction of Alterations in bile acid-independent flow and $Na^{+} - K^{+}$ - 84
ATPase activity do not always change in parallel (595, Ch
796). Thus, generation of this fraction of bile flow may sti
not depend on $Na^{+} - K^{+}$ -ATPase activit 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 796). Thus,
not depend
major ATP
hepatocyte
478, 509).
Alteration

Alterations in liver plasma membrane fluidity directly affects Na^+ -K⁺-ATPase activity. Fluidity has been in-
creased in rats pretreated with propylene glycol, thyroid hepatocyte has been suggested to be Mg^{++} -ATPase (317, of 478, 509).

21

21 Alterations in liver plasma membrane fluidity directly

21 affects Na^+ -K⁺-ATPase activity. Fluidity has been in-

21 creased in rats pretr 478, 509).

Alterations in liver plasma membrane fluidity direc

affects Na^+ -K⁺-ATPase activity. Fluidity has been

creased in rats pretreated with propylene glycol, thyre

hormone, and cortisone, decreased by ethinyl Alterations in liver plasma membrane fluidity direct
affects Na^+ -K⁺-ATPase activity. Fluidity has been in
creased in rats pretreated with propylene glycol, thyroi
hormone, and cortisone, decreased by ethinylestradic
a affects Na⁺-K⁺-ATPase activity. Fluidity has been in-
creased in rats pretreated with propylene glycol, thyroid
hormone, and cortisone, decreased by ethinylestradiol,
and unaffected by phenobarbital (595). The role of

D WATKINS
Recently, a method for isolating canalicular-enriched
plasma membranes has been reported (1033). The memplasma membranes has been reported (1033). The membranes has been reported (1033). The membranes has been reported (1033). The membranes exist as vesicles and are highly enriched in alke Branch WATKINS

Recently, a method for isolating canalicular-enriche

plasma membranes has been reported (1033). The mem

branes exist as vesicles and are highly enriched in alka

line phosphatase, Mg⁺⁺-ATPase and 5'-nuc Recently, a method for isolating canalicular-enriched
plasma membranes has been reported (1033). The mem-
branes exist as vesicles and are highly enriched in alka-
line phosphatase, Mg^{++} -ATPase and 5'-nucleotidase.
Phy plasma membranes has been reported (1033). The membranes exist as vesicles and are highly enriched in alka-
line phosphatase, Mg^{++} -ATPase and 5'-nucleotidase.
Physiological concentrations of micelle-forming bile
acids branes exist as vesicles and are highly enriched in alka-
line phosphatase, Mg^{++} -ATPase and 5'-nucleotidase.
Physiological concentrations of micelle-forming bile
acids reversibly inhibit both Mg^{++} - and Na^+ -K⁺-
A membranes in vienting 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 r hysiological concentrations of incene-forming one
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 actus Teversibly Infibit both Mg - and Na -R -
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 (9 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 studi

Recent studies in isolated perfused rat liver where 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 the ATFase (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 cheem to all one formation is understood (506).

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 for-

mati sodium ion is completely replaced by lithium ion indicate
that much of the basal bile acid-independent bile for-
mation is probably attributable to an ion pump other
than Na⁺-K⁺-ATPase (1202). Although Na⁺-K⁺-ATPas that much of the basal bile acid-independent bile for-
mation 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 mation is probably attributable to all foll pullp 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, 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 *2. Chloride* and *Bicarbonate Ion Secretion*. Transport 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-independen

not depend on $NA^+ - K^+ - ATP$ associated the 387). The peptide hormone secretin produces choleresis
major ATP-hydrolyzing enzyme at the biliary pole of the
hepatocyte has been suggested to be $Mg^{++} - ATP$ ase (317, of bile and 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 fract 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 2. Chloride and Bicarbonate Ion Secretion. Transport of anions other than bile acids may influence formation of the bile acid-independent fraction. Replacement chloride ion in the perfusate of the isolated rat liver wit in 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 norma chloride ion in the perfusate of the isolated rat liver with
nitrate ion decreases bile flow by 20% (411). After read-
mission of chloride ion, bile flow returns to normal thus
indicating that transport of chloride ion may mirate for decreases bie now 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
 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. Hardis mation is probably attributable to an ion pump other
than Na⁺-K⁺-A-TPase activity is depressed, (1902). Although Na⁺-K⁺-A-TPase
activity is depressed, bile acid and
dependent flow is not
influenced by complete rep determinant of secretion. Since the is an
antime 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
s **fram from the perfusate while 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 unaffec and Wood (465) observed a reduction in bile flow
sodium ion excretion when bicarbonate ion was remo
from the perfusate while bile acid elimination was us
fected. Bile flow rates were restored to control va
upon addition of sodium ion excretion when bicarbonate ion was removed
from the perfusate while bile acid elimination was unaf-
fected. Bile flow rates were restored to control values
upon addition of bicarbonate or dimethyloxazolidine-2,4 from the perfusate while bile acid elimination was unaf-
fected. Bile flow rates were restored to control values
upon addition of bicarbonate or dimethyloxazolidine-2,4-
dione, a weak, membrane-permeable adid capable of
tr iected. Bile how 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 t 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 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, hy-
drates, an transporting protons (465). Thus, bicarbonate transport
in the liver may involve a sodium-hydrogen exchange
system where CO_2 diffuses across the membrane, hy-
drates, and ionizes to $H^+ + HCO_3^-$. A proton is supplied
for in the liver may involve a sodium-hydrogen exchange
system where CO_2 diffuses across the membrane, hy-
drates, and ionizes to $H^+ + HCO_3^-$. A proton is supplied
for $Na^+ \text{-} H^+$ exchange diffusion and bicarbonate ion is
 system where CO_2 diffuses across the membrane, hy-
drates, and ionizes to $H^+ + HCO_3^-$. A proton is supplied
for $Na^+ \cdot H^+$ exchange diffusion and bicarbonate ion is
apparently transported into bile. Similar carrier syst for $Na^+ \text{-} H^+$ 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 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 (1 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
s mave been wen characterized in the rehal 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). 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 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). Er choleresis in the dog which is associated with an increase alkalinity of bile and total excretion of $HCO₃⁻$ (568, 940). Erythritol clearance measurements suggest the secretin-induced choleresis is of ductular ra of bile and total excretion of $HCO₃⁻$ (568, 940). Erythritol
clearance measurements suggest the secretin-induced
choleresis is of ductular rather than canalicular origin.
However, secretin has no effect on bile clearance measurements suggest the secretin-induced
choleresis is of ductular rather than canalicular origin.
However, secretin has no effect on bile flow or composi-
tion in the rat (309), yet Hardison and Wood (465)
demo choleresis is of ductular rather than canalicular oriation in the rat (309), yet Hardison and Wood (4 demonstrated a role of bicarbonate ion in bile format
in that species. Whether bicarbonate transport contributes to bile 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

PHARMACOLOGICAL REVIEWS

uncertain. Recent studies in cultured hepatocytes mdi-BILE FORMATION, HEPATIC UP
uncertain. Recent studies in cultured hepatocytes indi-
cate that sodium-coupled chloride transport may be im-
portant in the production of bile acid-independent flow BILE FORMATION, HEPATIC UPTAKE, a
uncertain. Recent studies in cultured hepatocytes indi-
cate that sodium-coupled chloride transport may be im-
gests
portant in the production of bile acid-independent flow Solut
(1037). H uncertain. Recent studies in cultured hepatocytes indicate that sodium-coupled chloride transport may be important in the production of bile acid-independent flow Soles (1037). However, no definitive evidence was presented reate that solutin-coupled contant in the production (1037). However, no definit
suggest that chloride transportion of basal bile flow.
3. Paracellular Fluid Flow. suggest that chloride transport accounts for a major

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 sol-
utes gain entrance into bile Spaces and associated incomplement of bases and associated paracellular Fluid Flow. Bile may also be formed via
the paracellular pathway where water and inorganic sol-
utes gain entrance into bile through the intercellular 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 dem-Interparacemular pathway where water and interparation-
utes gain entrance into bile through the intercellular
spaces and associated junctional complexes (126, 297,
720). Considerable electrophysiological evidence dem-
ons ques gain entrance mo bile through the intercentuar
spaces and associated junctional complexes (126, 297,
720). Considerable electrophysiological evidence dem-
onstrates certain epithelia with low electrical resistance
(i. spaces and associated junctional complexes $(120, 25, 720)$. Considerable electrophysiological evidence den onstrates certain epithelia with low electrical resistance (i.e., the jejunal epithelium) are "leaky" and their t t 20). Considerable electrophysiological evidence dem-
onstrates certain epithelia with low electrical resistance
(i.e., the jejunal epithelium) are "leaky" and their tight
junctions permit passage of fluid (370). Hepato (i.e., the jejunal epithelium) are "leaky" and their tight
junctions permit passage of fluid (370) . Hepatocyte junc-
tions have been classified as intermediate between tight
and leaky based on the number of associated m ments (1.e., the jejunal epithemini) are leaky and their tight
inntions permit passage of fluid (370). Hepatocyte junc-
ass
and leaky based on the number of associated microfila-
ments (365, 782). However, these structure differences being passage of find (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 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) dem and leaky based on the number of associated incromation
ments (365, 782). However, these structures appear to be
the errogeneous which may be important in the regulation
of functional permeability (702). Layden et al. (720 meterogeneous which may be important in the regula
of functional permeability (702). Layden et al. ('
demonstrated that dehydrocholate infusion increase
bile flow, 2) biliary clearance of [¹⁴C]sucrose, an inde
membrane p of functional permeability (102) . Layden et al. (120) defined
demonstrated that dehydrocholate infusion increased 1) ver
bile flow, 2) biliary clearance of $[$ ¹⁴C]sucrose, an index of proc
membrane permeability, an demonstrated that denyarocholate infusion increased if
bile flow, 2) biliary clearance of $[^{14}C]$ sucrose, an index comembrane permeability, and 3) incidence of invagina
tions of the intercellular surface membranes adjace bile flow, 2) biliary clearance of [¹⁴C]sucrose, an inde
membrane permeability, and 3) incidence of invagreement
tions of the intercellular surface membranes adjacen
the junctional complexes of hepatocytes. Similar n
pho membrane permeability, and 3) incluence of invagina-
tions of the intercellular surface membranes adjacent to
the junctional complexes of hepatocytes. Similar mor-
phological changes were observed after chronic taurocho-
l the junctional complexes of hepatocytes. Similar mor-
the junctional complexes of hepatocytes. Similar mor-
phological changes were observed after chronic taurocho-
late infusion (844). Metz and Bressler (803) noted that
t the junctional complexes of hepatocytes. Shimar
phological changes were observed after chronic taure
late infusion (844). Metz and Bressler (803) noted
the morphological changes in tight junctions induce
bile duct ligation photogical changes were observed after chronic tautocholate infusion (844). Metz and Bressler (803) noted that
the morphological changes in tight junctions induced by
bile duct ligation were reversible following reestablis 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 struc the morphological changes in tight junctions intuced by
bile duct ligation were reversible following reestablish
ment of the enterohepatic circulation. These data sugges
that hepatocyte tight junctions are not static struc evidence indicates that phalloidin 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 ment of the enteronepart circulation. These tasta suggest
that hepatocyte tight junctions are not static structures
but may respond to alterations in bile flow. Additiona
evidence indicates that phalloidin treatment increa that hepatocyte tight junctions are not static structure
but may respond to alterations in bile flow. Add
evidence indicates that phalloidin treatment inc
the permeability of the junctional complex which
trols the barriers It may respond to alterations in the now. Additional
idence indicates that phalloidin treatment increases
e permeability of the junctional complex which con-
bls the barriers to paracellular fluid flow (297).
Paracellular

Evidence indicates that phalloldin treatment increases
the permeability of the junctional complex which con-
trols the barriers to paracellular fluid flow (297).
Paracellular ion equilibration could occur at two sites:
bet trols 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 decreas raracentuar for equilibration collid 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, o between hepatotytes and/or in the duct epithena. Since
the surface/volume ratio of the biliary tree decreases
abruptly at the canaliculi-portal ductule junction, os-
motic equilibration in ductules or ducts is unlikely (35 delays abruptly at the canaliculi-portal ductule junction, os-
motic equilibration in ductules or ducts is unlikely (354).
Bile osmolarity is similar to that of red blood call-free
perfusates (150 to 450 mOsmol/l) in isola abidiply at the canancum-portar ducture junction, os-
motic 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 perfu motic 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
reted into bile $(232, 942, 960)$. Two benzimid Bile osmolarity is similar to that of fed blood centrice
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 du periusates (150 to 450 mosilior)? In isolated periused

rat liver thereby indicating that bile must attain osmotic

equilibrium at the hepatocyte (124) because bile ducts

are functionally inactive and do not permit exchan equilibrium at the hepatocyte (124) because bile ducts
are functionally inactive and do not permit exchange of
²⁴Na or ³⁶Cl (411). The permeability barrier to ion entry
depends on ion species. The sequence for cations equinorium at the hepatocyte (124) because bile ducts
are functionally inactive and do not permit exchange of
²⁴Na or ³⁶Cl (411). The permeability barrier to ion entry
depends on ion species. The sequence for cations are functionally inactive and do not permit exchange of

²⁴Na or ³⁶Cl (411). The permeability barrier to ion entry

depends on ion species. The sequence for cations is

lithium > sodium > potassium > Tris > choline, a Na or C1 (411). The permeability barrier to for 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
P depends on form species. The sequence is
lithium > sodium > potassium > Tris > cho
anions is nitrate > chloride > acetate > sulfa
Peterlik (411) concluded these ions enter bil
the junctional complex from blood to bile.
Sel 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 mem-

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 mem-

b charged and uncharged weight-matched solute pairs

([carboxyl-¹⁴C]inulin and [methoxy-³H]inulin, and $[{}^{14}C]$

ferrocyanide and ${}^{8}C$] [${}^{14}C$]

ferrocyanide and ${}^{8}C$] [${}^{14}C$]

ferrocyanide and ${}^{8}C$] [Selective permeability of the binary candidariled
brane has been evaluated by measuring the clearance of
charged and uncharged weight-matched solute pairs
([carboxyl-¹⁴C]inulin and [methoxy-³H]inulin, and [¹⁴C]
ferro Selective permeability of the bilary candicular mem-

brane has been evaluated by measuring the clearance of

charged and uncharged weight-matched solute pairs

([carboxyl-¹⁴C]inulin and [methoxy-³H]inulin, and $[{}^{14$

(1037). However, no definitive evidence was presented to bile acid excretion rates thus implying that bile acids did
suggest that chloride transport accounts for a major not generate a significant negative potential in the biliary clearance for the negatively charged species suggests there is an electrical barrier to anion movement. KE, AND BILIARY EXCRETION
biliary clearance for the negatively charged species suggests there is an electrical barrier to anion movement.
Solute pair clearance ratios were constant over changin SOLUTE PAIR PROPERTION 9

biliary clearance for the negatively charged species sug-

gests there is an electrical barrier to anion movement.

Solute pair clearance ratios were constant over changing

bile acid excretion ra 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 acid gests there is an electrical barrier to amon 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 t bile acid excretion rates thus implying that bile acids did bile acid excretion rates thus implying that bile acids did
not generate a significant negative potential in the can-
alicular lumen. Clearance of methoxyinulin and the
much smaller molecule sucrose were similar, suggestin not generate a significant negative potential in the can-
alicular lumen. Clearance of methoxyinulin and the
much smaller molecule sucrose were similar, suggesting
identical channels for both solutes which are much larger
 ancular lumen. Clearance of methoxymuln 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 e 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 thes an the pores that admit water and smaller solutes such erythritol. Bradley and Herz (130) estimated these
annels represent 10% of the surface area available for
ter movement.
4. *Microfilaments and Microtubules*. Microfila

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 hepatocyt water movement.
4. Microfilaments and Microtubules. Microfilaments
associated with actin are found in hepatocytes (363) at
the cytoplasmic face of the plasma membrane, particu-
larly around canaliculi where a thin network 4. Microfilaments and Microtubules. Microfilaments
associated with actin are found in hepatocytes (363) at
the cytoplasmic face of the plasma membrane, particu-
larly around canaliculi where a thin network extends into
the associated with actin are found in hepatocytes (363) at
the cytoplasmic face of the plasma membrane, particu-
larly around canaliculi where a thin network extends into
the microvilli (375, 862). Microfilaments derive from varity around canaliculi where a thin network extends into
the microvilli (375, 862). Microfilaments derive from the
globular protein actin and are responsible for the con-
tractile functions of many cells. Phalloidin caus 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 hepatocyte versible 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 f versible polymerization of actin into incrofilaments thus
producing hyperplasia of actin filaments in hepatocytes
and a decreased bile flow (268, 297, 374, 408, 1189).
Cytochalasin B specifically inhibits the contractile f producing hyperplasia of actin maments in nepatocytes
and a decreased bile flow (268, 297, 374, 408, 1189).
Cytochalasin B specifically inhibits the contractile func-
tion of microfilaments and produces a thickening of
mic and a decreased one now (208, 297, 374, 408, 1189).
Cytochalasin B specifically inhibits the contractile func-
tion of microfilaments and produces a thickening of
microfilaments within the pericanalicular ectoplasm, a
loss on of microfilaments and produces a thickening of icrofilaments within the pericanalicular ectoplasm, as so f microvilli from bile canaliculi, and a decreased le flow in the perfused rat liver (919).
Microtubules consist a

micromaments within the pericanalicular ectoplas
loss of microvilli from bile canaliculi, and a decre
bile flow in the perfused rat liver (919).
Microtubules consist almost exclusively of polyn
tubulin. Colchicine, an inhi loss of microvilli from bile canaliculi, and a decreas
bile flow in the perfused rat liver (919).
Microtubules consist almost exclusively of polymer
tubulin. Colchicine, an inhibitor of tubulin polymeriz
tion, causes an al one now in the periused rat liver (515).
Microtubules consist almost exclusively of polymetubulin. Colchicine, an inhibitor of tubulin polymerition, causes an almost complete disappearance of mic
tubules and decreases bile Microtubules consist almost exclusively of polymeric
tubulin. Colchicine, an inhibitor of tubulin polymeriza-
tion, causes an almost complete disappearance of micro-
tubules and decreases bile acid secretion (269). Colchitubulm. Colcineme, an immotor of tubulm polymerization, causes an almost complete disappearance of microtubules and decreases bile acid secretion (269). Colchicine also inhibits secretion of lipoproteins and proteins into diffusive and decreases one acid secretion (209). Coloni-
cine also inhibits secretion of lipoproteins and proteins
into the serum (269, 1130). Combined administration of
phalloidin: and colchicine synergistically increase cine 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 dis nto the serum (269, 1130). Combined administration or
phalloidin and colchicine synergistically increases the
pericanalicular microfilamentous network and the dis-
appearance of microtubules and decreases basal bile flow
(phanological and colonicine synergistically increases the
pericanalicular microfilamentous network and the dis-
appearance of microtubules and decreases basal bile flow
(269). Agents that decrease microtubular function, su appearance of microtubules and decreases basal bile how
(269). Agents that decrease microtubular function, such
as vinblastine, vincristine, and colchicine, also cause
hepatic accumulation of small secretory vesicles conta (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 e as vinduastine, vincristine, and colemente, also depatic accumulation of small secretory vesicles con
ing proteins and triacylglycerol which are normally
creted into bile (232, 942, 960). Two benzimidazole
bamates, nocadoz mepatic 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 antimicrotubula creted into bile (232, 942, 960). Two benzimidazole car-
bamates, nocadozle and parbendazole, with antimicro-
tubular activity block the biliary secretion of albumin
and triacylglycerol by isolated hepatocytes (108); this
 excretion. the cytoplasmic face of the plasma membrane, particu-
larly around canaliculi where a thin network extends into
the microvilli (375, 862). Microfilaments derive from the
globular protein actin and are responsible for the

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 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 hepa 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 biliary lipid secretion (419). In fact, rat hepatocytes in primary culture show dynamic contractions of bile can-
aliculi by actin-containing microfilaments which may The ductular-ductular-ductular-ductular-ductular-ductular-ductular-ductular-ductular-ductular-ductular-ductular-ductular-ductular-ductular-ductular-ductular-ductular-ductular-ductular-ductular-ductular-ductular-ductular-du

D. Ductular Modification of Canalicular Bile

influence bile production (920).

D. Ductular Modification of Canalicular Bile

The ductular-ductal system can alter electrolyte com-

position and volume of canalicular bile by reabsorption

and/or secretion of water. Sec

PHARMACOLOGICAL REVIEWS

10
active bicarbonate excretion (177, 350, 1148) and possibly
an electroneutral sodium chloride pumping mechanism
al 10

active bicarbonate excretion (177, 350, 1148) and possibly man

an electroneutral sodium chloride pumping mechanism slow

(105). The quantitative contribution of ductular secre-

tion KLAASSEN

active bicarbonate excretion (177, 350, 1148) and possib

an electroneutral sodium chloride pumping mechanis

(105). The quantitative contribution of ductular secre-

tion to total bile flow is highly species-dep active bicarbonate excretion (177, 350, 1148) and possil
an electroneutral sodium chloride pumping mechanii
(105). The quantitative contribution of ductular section to total bile flow is highly species-dependent. Inter-
mi active bicarbonate excretion (177, 350, 1148) and possibly man electroneutral sodium chloride pumping mechanism slow
(105). The quantitative contribution of ductular secretion
tion to total bile flow is highly species-depe an electroneutral sodium chloride pumping mechanism
(105). The quantitative contribution of ductular secre-
tion to total bile flow is highly species-dependent. Inter-
mittent feeders, such as dogs and humans, have an
impo (105). The quantitative contribution of ductular secretion to total bile flow is highly species-dependent. Inter-
mittent feeders, such as dogs and humans, have an comportant ductular component, while continuous eaters, 9 tion to total bile flow is highly species-dependent. Inter-
mittent feeders, such as dogs and humans, have an
important ductular component, while continuous eaters,
such as most rodents, have a negligible contribution of
t mittent 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 r important ductular component, while continuous eaters,
such as most rodents, have a negligible contribution of
the collecting system to bile flow (354). The concentra-
tion ratios of erythritol in bile to plasma are as fol such as most rodents, have a negligible contribution
the collecting system to bile flow (354). The concention ratios of erythritol in bile to plasma are as folld
dog, 2.3; rabbit, 1.2; rat, 0.9; and guinea pigs, 0.7 (3
350 the collecting system to bile flow (354) . The concentra-
tion 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 in tion ratios of erythritol in bile to plasma are as follows: E .
dog, 2.3; rabbit, 1.2; rat, 0.9; and guinea pigs, 0.7 (311,
350, 356, 623, 632, 1254). These data indicate consider-
able ductular reabsorption in dogs, som 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 but reabsorption in rat, and some ductular secreti 350, 356, 623, 632, 1254). These data indicate consider-
able 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 able ductular reabsorption in dogs, some in rabbits, no
reabsorption in rat, and some ductular secretion in 354 , 5
guinea pigs. The ratio in humans is between 0.27 and
0.43, indicating pronounced ductular secretion (125 reabsorption in rat, and some ductular secretion
guinea pigs. The ratio in humans is between 0.27 a
0.43, indicating pronounced ductular secretion (125, 7
938). Rodents have high rates of spontaneous bile fl
(50 to 90 μ fractions. 43, indicating pronounced ductular secretion (125, 7
8). Rodents have high rates of spontaneous bile fl
0 to 90 μ l/min/kg) and large bile acid-independ
actions.
Many gastrointestinal hormones, which exert physical cont

938). Rodents have high rates of spontaneous bile flot (50 to 90 μ l/min/kg) and large bile acid-independe fractions.
Many gastrointestinal hormones, which exert physical control of gastric acid secretion, intestinal mo (50 to 90 μ /min/kg) and large bile acid-independent definations.

Many gastrointestinal hormones, which exert physio-

logical control of gastric acid secretion, intestinal motil-

ity, and gallbladder contraction, can fractions.

Many gastrointestinal hormones, which exert physio-

logical control of gastric acid secretion, intestinal motil-

ity, and gallbladder contraction, can also influence bile

composition and volume during eating Many gastrointestinal hormones, which exert physio-
logical control of gastric acid secretion, intestinal motil-
ity, and gallbladder contraction, can also influence bile
composition and volume during eating and digestion composition and volume during eating and digestion and 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 circulatio 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 bil and the enterohepatic cycle of bile acids.
controlled interruption of the enterohepatic
(261) and comparison of fed versus fasted s
production in primates (1150) emphasize the
of eating on variations in ductular secretion. ntrolled interruption of the enterohepatic circulat
61) and comparison of fed versus fasted state on loduction in primates (1150) emphasize the importation
eating on variations in ductular secretion.
The best evidence for

production in primates (1150) emphasize the importance
of eating on variations in ductular secretion.
The best evidence for ductal modification of canalic-
ular bile is that the pancreatic peptide secretin stimulates
bile production in primates (1150) emphasize the importance
of eating on variations in ductular secretion.
The best evidence for ductal modification of canalic-
ular bile is that the pancreatic peptide secretin stimulates
bile of eating on variations in ductular secretion.
The best evidence for ductal modification of canalic-
ular bile is that the pancreatic peptide secretin stimulates
bile formation in isolated bile ducts of dogs (832) thus
pro ular 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, ular 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, 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 transien producing an abrupt negativity in the lumenal membrane
potential indicative of active anion transport, possibly
 $HCO₃^-$. In addition, analysis of excretory transients after
selective arterial injections of secretin s 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 slight $HCO₃$. 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 (463). Exercise of action (1251). Bile becomes slightly hypertonic

ring secretin choleresis (940) which probably results

om increased excretion of chloride and bicarbonate ions

63).

Reabsorption and secretion of water and ele

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, especia 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 r (463).
Reabsorption and secretion of water and electroly
can be performed by ductular epithelium, especially aft
cholinergic blockade in dogs (1254) and resection of t
antrum and small bowel in monkeys (1148); both proc
d 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 proce-
 can be performed by ductular epithelium, especiall
cholinergic blockade in dogs (1254) and resection
antrum and small bowel in monkeys (1148); both
dures suppress hormone-mediated secretion. A co
amount of water is reabsor cholinergic blockade in dogs (1254) and resection of the antrum and small bowel in monkeys (1148); both proce-
dures suppress hormone-mediated secretion. A constant amount of water is reabsorption during taurocholate-in-
d antrum and small bowel in monkeys (1148); both produres suppress hormone-mediated secretion. A constantion of water is reabsorbed during taurocholateduced choleresis (74), suggesting that fluid reabsorpt occurs independent dures suppress hormone-mediated secretion. A constant amount of water is reabsorbed during taurocholate-in-
duced choleresis (74), suggesting that fluid reabsorption
occurs independently of bile flow. In dogs, the concen-
 amount of water is reabsorbed during taurocholate-in-
duced choleresis (74), suggesting that fluid reabsorption
occurs independently of bile flow. In dogs, the concen-
trative capacity of the common bile duct increases aft duced choleresis (74), suggesting that fluid reabsorption
occurs independently of bile flow. In dogs, the concen-
trative capacity of the common bile duct increases after
cholecystectomy (1253). After surgery and an overni 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 severa trative capacity of the common bile duct increases after where
cholecystectomy (1253). After surgery and an overnight in fast, extrahepatic ducts are enlarged and contain several 7
milliliters of bile similar in compositi cholecystectomy (1253). After surgery and an overnight in fast, extrahepatic ducts are enlarged and contain several 73 milliliters of bile similar in composition to gallbladder (16) bile. Ductal reabsorption appears to be 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 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 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.

mans may actively reabsorb glucose (447, 872, 873) and D WATKINS
mans may actively reabsorb glucose (447, 872, 873) an
slowly reabsorb urea (911). Retrograde intrabiliary injec-
tion experiments indicate extensive absorption of wate D WATKINS
mans may actively reabsorb glucose (447, 872, 873) and
slowly reabsorb urea (911). Retrograde intrabiliary injec-
tion experiments indicate extensive absorption of water,
morphine, and BSP. The latter two undergo mans may actively reabsorb glucose (447, 872, 873) and
slowly reabsorb urea (911). Retrograde intrabiliary injec-
tion experiments indicate extensive absorption of water
morphine, and BSP. The latter two undergo subsequent mans may actively reabsorb glucose (447, 872, 873) and
slowly reabsorb urea (911). Retrograde intrabiliary injec-
tion experiments indicate extensive absorption of water,
morphine, and BSP. The latter two undergo subsequen slowly reabsorb urea (911). Retrograde intrabiliary in
tion experiments indicate extensive absorption of wa
morphine, and BSP. The latter two undergo subsequ
conjugation and biliary excretion (371, 534, 872, 8
911–913). Wh tion 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 predomi-
nate unknown. **E. Neurohumoral Control of Bile Formation**
E. Neurohumoral Control of Bile Formation
E. Neurohumoral Control of Bile Formation
There are numerous factors that influence the under normal physiological conditions, however, is

inknown.

Neurohumoral Control of Bile Formation

There are numerous factors that influence bile flow

it whose sites of action are unknown (306, 307, 309,

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, 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, E. Neurohumoral Control of Bile
There are numerous factors t
but whose sites of action are un
354, 570, 970). These factors inconsered
wascular pressure, and hormones
Nerve fibers are abundant with There are numerous factors that influence bile flow
it whose sites of action are unknown (306, 307, 309,
4, 570, 970). These factors include neural influences,
scular pressure, and hormones.
Nerve fibers are abundant with

ity, and gallbladder contraction, can also influence bile

ity, and gallbladder contraction, can also influence bile

composition and volume during eating and digestion and

hence affect the choleretic properties of these 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 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 influen 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, al 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 pervessels, bile ductules, and ducts (359, 1152). Whethe
these nerves influence bile flow directly has not bee
determined. However, alterations in hepatocellular per
fusion induced by nerve stimulation could influence bil
for these nerves influence bile flow directly has not been
determined. However, alterations in hepatocellular per-
fusion induced by nerve stimulation could influence bile
formation by affecting the counterflow arrangement
(1 determined. However, alterations in hepatocellular per-
fusion induced by nerve stimulation could influence bile
formation by affecting the counterflow arrangement
(1135). A direct effect of vagal tone on bile flow has bee fusion induced by nerve stimulation could influence bil
formation by affecting the counterflow arrangemen
(1135). A direct effect of vagal tone on bile flow has bee
suggested since truncal vagotomy decreases spontaneou
bic formation by affecting the counterflow arrangeme (1135) . A direct effect of vagal tone on bile flow has be suggested since truncal vagotomy decreases spontaneo bicarbonate secretion and reduces insulin-induced cheresis (1135). A direct effect of vagal tone on bile flow has been
suggested since truncal vagotomy decreases spontaneous
bicarbonate secretion and reduces insulin-induced chol-
eresis (407, 579). Apparently, considerable specie suggested since truncal vagotomy decreases spontaneous
bicarbonate secretion and reduces insulin-induced chol-
eresis (407, 579). Apparently, considerable species differ-
ences exist as stimulation of the vagus influences bicarbonate secretion and reduces insulin-induced choleresis (407, 579). Apparently, considerable species differences exist as stimulation of the vagus influences bil flow in man (60) and dogs (367, 383, 579, 924, 1161) bu eresis (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 ences 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 chol-
eresis is observed after dopamine administrat Nerve mores 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 pe has no effect in rabbits and cats (1161). Although
eresis is observed after dopamine administration
adrenergic control mechanisms are even less unde
than are vagal effects. It is also difficult to d
whether these effects r eresis 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 neurotransmi adrenergic control mechanisms are even less understocthan are vagal effects. It is also difficult to discervant
between these effects result directly from neurotransmiters or from indirect neural influences mediated by a
t than are vags
whether these
ters or from it
terations in pe
bolic changes.
Bile flow is 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 variatio

ters 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 pr terations 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 bolic changes.
Bile flow is largely unaffected by variations in hepatic
blood flow rate once a critical opening pressure is at-
tained (136, 137). In contrast, released hormones can
produce marked changes in bile flow (354 Bile flow is largely unaffected by variations in hepatic
blood flow rate once a critical opening pressure is at-
tained (136, 137). In contrast, released hormones can
produce marked changes in bile flow (354, 570, 970). Fo 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 pr 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 hormon 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 hormo example, gastrin (1294) and histamine (582) stimulate $\frac{3}{5}$
production of bile with high bicarbonate and chloride ion
concentrations, respectively. Gastrointestinal hormones
that stimulate flow are listed in decreasin 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 concentrations, respectively. Gastrointestinal horn
that stimulate flow are listed in decreasing ord
potency: cholecystokinin, caerulein, pentagastrin
gastrin II (569, 578, 580). Sulfated gastrin II, bu
gastrin I, is chole 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 ph potency: ch
gastrin II (*f*
gastrin I, is
physiologica
flow (568).
Hydrocort 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 hepatocellul

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 (7 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 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 pi 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 rabbi 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. Whet insulin, glucagon also stimulates bile flow in man 730) and dogs (581), but not in guinea pigs and ra
(1079), by apparently increasing cAMP levels. Whe
glucagon stimulates canalicular or ductular bile flow
not been determi 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 (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 hormone glucagon stimulates canalicular or ductular bile flow
not been determined. Thyroidectomy and hypophy
tomy decrease bile flow (623, 717). Thus, numerous
mones have profound actions on the elaboration of
and biliary flow by

BILE FORMATION, HEPATIC UPTAKE, AND BILIARY EXCRETION
Bile flow, biliary concentrations, and excretion rates bile acid-independent flow m
of bile acid, cholesterol, and phospholipid follow a cir- bile acids (635). cadian rhythm in rats with a peak at midnight and a BILE FORMATION, HEPATIC UPTAKE

cadian rhythm in rats with a peak at midnight and a

rhythm in rats with a peak at midnight and a

rhythm in rats with a peak at midnight and a

rhythm in rats with a peak at midnight and a
 Bile flow, biliary concentrations, and excretion reportion (57, 59, 267, 491, 1214). Bile acid-independent flow is maximal during the night and example Bile flow, biliary concentrations, and excretion rates bile
of bile acid, cholesterol, and phospholipid follow a cir-
cadian rhythm in rats with a peak at midnight and a
nadir at noon (57, 59, 267, 491, 1214). Bile acid-in of bile acid, cholesterol, and phospholipid follow a cadian rhythm in rats with a peak at midnight and nadir at noon (57, 59, 267, 491, 1214). Bile acid-in pendent flow is maximal during the night and eamorning (57, 59). B cadian rhythm in rats with a peak at midnight and a
nadir at noon $(57, 59, 267, 491, 1214)$. Bile acid-inde-
pendent flow is maximal during the night and early
morning $(57, 59)$. Biliary transport maximum for dibrom-
op pendent flow is maximal during the night and early
morning (57, 59). Biliary transport maximum for dibrom-
ophthalein disulfonate (DBSP) was 25% higher at night
than at noon (1214, 1217). In addition, food intake stim-
ula pendent flow is maximal during the night and early abmorning (57, 59). Biliary transport maximum for dibrom-
ophthalein disulfonate (DBSP) was 25% higher at night the
than at noon (1214, 1217). In addition, food intake sti circadian rhythm of bile secretion (801).
V. Alteration of Bile Formation **EXECUTE:** Was 23% figher at 1
 V. (1214, 1217). In addition, food intake is
 P. flow and appears to be a major factor is
 P. flow and appears to be a major factor is
 V. Alteration of Bile Formation

Prodogenous c

Many endogenous compounds and xenobiotics in-
Many endogenous compounds and xenobiotics in-
asse or decrease bile flow and are referred to as chol-**Example 10 Telecom COVERT**
 CREASE OF STATE FORMATION

Many endogenous compounds and xenobiotics in

crease or decrease bile flow and are referred to as choleretic and cholestatic agents, respectively. Bile flow rat V. Alteration of Bile Formation or
or Many endogenous compounds and xenobiotics in-
crease or decrease bile flow and are referred to as chol-
eretic and cholestatic agents, respectively. Bile flow rate
may be expressed rel Many endogenous compounds and xenobiotics in-
crease or decrease bile flow and are referred to as chol-
eretic and cholestatic agents, respectively. Bile flow rate
may be expressed relative to body weight or liver weight
(Many endogenous compounds and xenobiot
crease or decrease bile flow and are referred to a
eretic and cholestatic agents, respectively. Bile flow
may be expressed relative to body weight or liver
(usual methods) or hepatic **Exercic and chole may be expressed**
 A. Choleresis
 A. Choleresis
 A. chemical c.

A chemical can increase bile flow by stimulating the
and methods) or hepatic DNA content (811).
Choleresis po
A chemical can increase bile flow by stimulating the $\frac{\text{sev}}{\text{win}}$
and secretion of biliary constituents and (usual methods) or nepatic DNA content (611).

A. Choleresis pour

A chemical can increase bile flow by stimulating the sevent

manufacture and secretion of biliary constituents and by

biliary excretion of the chemical a A. Choleresis
A chemical can increase bile flow by stimulating the
manufacture and secretion of biliary constituents and b
biliary excretion of the chemical and/or its metabolites.
1. Bile Acids. The acute effect of bile a *A* chemical can increase bile flow by stimulating the

invision-

intervention of the chemical and/or its metabolites.
 1. Bile Acids. The acute effect of bile acids on bile

doduction has been extensively examined. Pre

A chemical can increase bile flow by stimulating th
manufacture and secretion of biliary constituents and b
biliary excretion of the chemical and/or its metabolites
1. Bile Acids. The acute effect of bile acids on bil
prod 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 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
 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. Recen production has been extensively examined. Presum
choleresis results from the osmotic gradient create
excretion of bile acids into the canalicular lumen. Re
studies in rats indicate the following choleretic poter
in decreas 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 > cheno excretion of bile acids into the canalicular lumen. Recent
studies in rats indicate the following choleretic potencies
in decreasing order: dehydrocholic acid > chenodeoxy-
cholic acid > cholic acid > taurocholic acid > d studies in rats indicate the following choleretic potencies
in decreasing order: dehydrocholic acid > chenodeoxy-
cholic acid \ge cholic acid > taurocholic acid > deoxycholic
acid > glycocholic acid (337, 877). Similar r in decreasing order: dehydrocholic acid $>$ chenodeox cholic acid \geq cholic acid $>$ decay decay cholic acid \geq glycocholic acid (337, 877). Similar results have been observed in dogs (624, 630). The volume of wat e cholic acid \ge cholic acid $>$ taurocholic acid \ge deoxycholic
acid \ge glycocholic acid (337, 877). Similar results have
been observed in dogs (624, 630). The volume of water
excreted per micromole of bile acid (est 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 calcu-
lating the slope of the relation between bile flow an 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 excreted per micromole of bile acid (estimated by calculating the slope of the relation between bile flow and bile mic
acid excretion; fig. 4) depends on species and bile acid. For Staurocholic acid it is 8 μ l in dogs lating 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 μ l in dogs (940, 1254), 13 μ l in
rhesus monkeys (261), 15 μ l in r acid excretion; fig. 4) depends on species and bile acid.For
taurocholic acid it is 8 μ l in dogs (940, 1254), 13 μ l in
rhesus monkeys (261), 15 μ l in rats (102, 1080), 30 μ l in
rabbits (310), and 26 μ l in g taurocholic acid it is 8 μ l in dogs (940, 1254), 13 μ l in chreasus monkeys (261), 15 μ l in rats (102, 1080), 30 μ l in (3*th*) rabbits (310), and 26 μ l in guinea pigs (1080). In the rat 2,4 and rabbit, bile rhesus monkeys (261), 15 μ l in rats (102, 1080), 30 μ l in rabbits (310), and 26 μ l in guinea pigs (1080). In the rat $2,4$ and rabbit, bile acids can produce a two- to threefold on increase in bile flow while in rabbits (310), and 26 μ l in guinea pigs (1080). In the and rabbit, bile acids can produce a two- to three increase in bile flow while in the dog they increase flow six- to sevenfold (624). These differences are large d and rabbit, bile acids can produce a two- to threefold increase in bile flow while in the dog they increase bile (252)
flow six- to sevenfold (624). These differences are largely cule
due to the much lower basal bile fl 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. Dehydro-
cholate produces a higher bile flow which is tho flow six- to sevenfold (624). These differences are largely
due to the much lower basal bile flow in dogs. Dehydro-
cholate produces a higher bile flow which is thought to
be related to its lower tendency to form micelles due to the much lower basal bile flow in dogs. Dehydro-
cholate produces a higher bile flow which is thought to
be related to its lower tendency to form micelles (243, ist
1080, 1114) since the osmotic potency of micelle-f cholate 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 b be related to its lower tendency to form micelles $(243, 1080, 1114)$ since the osmotic potency of micelle-forming of t
bile acids is lower than that of non-micelle-forming bile volu
acids (461) . More recent studies sug 1080, 1114) since the osmotic potency of micelle-form
bile acids is lower than that of non-micelle-forming
acids (461). More recent studies suggest that the c
eretic potency of bile acids is not inversely relate
their abil le acids is lower than that of non-micelle-forming bile
ids (461). More recent studies suggest that the chol-
etic potency of bile acids is not inversely related to
eir ability to form micelles (337, 630, 875, 1067).
The b

acids (461). More recent studies suggest that the chol-
eretic potency of bile acids is not inversely related to μ
their ability to form micelles (337, 630, 875, 1067). ((
The bile flow during bile acid choleresis ofte eretic potency of bile acids is not inversely related to μ n
their ability to form micelles (337, 630, 875, 1067). (di
The bile flow during bile acid choleresis often exceeds ion
that which would be theoretically accoun The bile flow during bile acid choleresis often exceeds ion
that which would be theoretically accounted for by simple V₈
osmotic activity of the bile acid in bile. This extra bile 7¹
may be formed either by effects on that which would be theoretically accounted for by simple Va
osmotic activity of the bile acid in bile. This extra bile 7 t
may be formed either by effects on an electrolyte pump other
or by decreased reabsorption of flui 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 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 μ /min/kg if fluid reabsorpt

NKE, AND BILIARY EXCRETION 11
bile acid-independent flow may also be stimulated by
bile acids (635). KE, AND BILIARY
bile acid-indepen
bile acids (635).
Another factor

E, AND BILIARY EXCRETION 11
le acid-independent flow may also be stimulated by
le acids (635).
Another factor important in determining differences
bile acid-induced increases in bile flow is the permebile acid-independent flow may also be stimulated
bile acids (635).
Another factor important in determining different
in bile acid-induced increases in bile flow is the perm
ability (conductivity) of the canalicular epithe 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 perme-
ability (conductivity) of the canalicular bile acids (635).

Another factor important in determining differences

in bile acid-induced increases in bile flow is the perme-

ability (conductivity) of the canalicular epithelium to

water and inorganic ions. This fac Another factor important in determining differences in bile acid-induced increases in bile flow is the perm ability (conductivity) of the canalicular epithelium water and inorganic ions. This factor is thought to \vert the in bile acid-induced increases in bile flow is the perme-
ability (conductivity) of the canalicular epithelium to
water and inorganic ions. This factor is thought to be
the most important determinant of interspecies variaability (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 repr water and inorganic ions. This factor is thought to be
the most important determinant of interspecies varia-
tions in bile flow (1246, 1247), but probably does not
represent a major mechanism for bile acid choleresis
(875) the most important determinant of interspecies varia-
tions 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 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 flo (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, thes mechanisms. reeded the theoretical value for an osmotic choleresis
2. Other Organic Compounds. Numerous xenobiotics
2. *Other Organic Compounds.* Numerous xenobiotics
cluding organic anions, cations, and neutral com-

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, bile acids apparently stimulate bile flow by at least two
mechanisms.
2. Other Organic Compounds. Numerous xenobiotics
including organic anions, cations, and neutral com-
pounds are capable of producing a choleresis in one bile acids apparently stimulate bile flow by at least two
mechanisms.
2. Other Organic Compounds. Numerous xenobiotics
including organic anions, cations, and neutral com-
pounds are capable of producing a choleresis in one mechanisms.

2. Other Organic Compounds. Numerous xenobiotics

including organic anions, cations, and neutral com-

pounds are capable of producing a choleresis in one or

several species of animals. Basal bile flow rate v 2. Other Organic Compounds. Numerous xenobiotics
including organic anions, cations, and neutral com-
pounds are capable of producing a choleresis in one or
several species of animals. Basal bile flow rate varies
widely fr 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 5μ /min/kg in dogs to 60 in rats and rabbits, several species of animals. Basal bile flow rate varies
widely from 5μ l/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 several species of animals. Basal bile flow rate varies widely from 5μ l/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 s widely from 5μ l/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 in 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 two-
fold in rats and rabbits and six-fold in dogs by effect of a xenobiotic partly depends on the species and
its basal flow. For example, bile flow is increased two-
fold in rats and rabbits and six-fold in dogs by cholic,
taurocholic, and dehydrocholic acids (624). In gene its basal flow. For example, bile flow is increased two-
fold in rats and rabbits and six-fold in dogs by cholic,
taurocholic, and dehydrocholic acids (624). In general,
BSP, eosine, fluorescein, ioglycamide, phenol red, a fold in rats and rabbits and six-fold in dogs by cholic taurocholic, and dehydrocholic acids (624). In genera
BSP, eosine, fluorescein, ioglycamide, phenol red, an
phlorizin are choleretic and increase bile production b
th taurocholic, and dehydrocholic acids (624). In genera
BSP, eosine, fluorescein, ioglycamide, phenol red, an
phlorizin are choleretic and increase bile production b
the osmotic activity of the chemical in bile (309). How
ev BSP, eosine, fluorescein, ioglycamide, phenol red, and phlorizin are choleretic and increase bile production b
the osmotic activity of the chemical in bile (309). How
ever, the effect of these compounds on bile flow is dos phlorizin are choleretic and increase bile production by
the osmotic activity of the chemical in bile (309). How-
ever, the effect of these compounds on bile flow is dose-
dependent. For example, low doses of BSP produce c the osmotic activity of the
ever, the effect of these complees, the effect of these complesed
erestatic in dogs (493), but
mice (428) are cholestatic
Several xenobiotics sue er, the effect of these compounds on bile flow is dose
pendent. For example, low doses of BSP produce chol
esis in dogs (493), but higher doses in rats (948) an
ice (428) are cholestatic.
Several xenobiotics such as proben

their ability to form micelles (337, 630, 875, 1067). (diethyl maleate, 13 μ l in rat and 17 μ l in dog; iodipamide,
The bile flow during bile acid choleresis often exceeds iodoxamate, and ioglycamide, 22 μ ; valpro dependent. For example, low doses of BSP produce cholenesis in dogs (493), but higher doses in rats (948) and mice (428) are cholestatic.
Several xenobiotics such as probenecid (314), etha-
crynic acid (178, 658), diethyl eresis in dogs (493), but higher doses in rats (948) amice (428) are cholestatic.

Several xenobiotics such as probenecid (314), et

crynic acid (178, 658), diethyl maleate (73), iodipam

(342), iodoxamate (96, 329), iogly mice (428) are cholestatic.

Several xenobiotics such as probenecid (314),

crynic acid (178, 658), diethyl maleate (73), iodipi

(342), iodoxamate (96, 329), ioglycamide (750), 1-cl

2,4-dinitrobenzene-5-glutathione (1225 Several xenobiotics such as probenecid (314), etha-
crynic acid (178, 658), diethyl maleate (73), iodipamide
(342), iodoxamate (96, 329), ioglycamide (750), 1-chloro-
2,4-dinitrobenzene-5-glutathione (1225), BSP-glutathi-
 crynic acid (178, 658), diethyl maleate (73), iodip
(342), iodoxamate (96, 329), ioglycamide (750), 1-c
2,4-dinitrobenzene-5-glutathione (1225), BSP-glu
one (71, 340), dihydroxydibutyl ether (215), valproi
(252, 253, 1234, (342), iodoxamate (96, 329), ioglycamide (750), 1-chlorc 2,4-dinitrobenzene-5-glutathione (1225), BSP-glutathione (71, 340), dihydroxydibutyl ether (215), valproic aci (252, 253, 1234, 1236), naltrexone (995), 6,7-dimethy 2,4-dinitrobenzene-5-glutathione (1225), BSP-glutathione (71, 340), dihydroxydibutyl ether (215), valproic acid (252, 253, 1234, 1236), naltrexone (995), 6,7-dimethylles-culetin (1158), and genipin and patrinoside (1159) s one (71, 340), dihydroxydibutyl ether (215), valproic a
(252, 253, 1234, 1236), naltrexone (995), 6,7-dimethyll
culetin (1158), and genipin and patrinoside (1159) sti
ulate bile flow in rats or dogs. Choleresis induced
the (252, 253, 1234, 1236), naltrexone (995), 6,7-dimethylles-
culetin (1158), and genipin and patrinoside (1159) stim-
ulate bile flow in rats or dogs. Choleresis induced by
these compounds occurs immediately after acute adm culetin (1158), and genipin and patrinoside (1159) stim-
ulate bile flow in rats or dogs. Choleresis induced by
these compounds occurs immediately after acute admin-
istration and is predominantly due to the osmotic activi ulate bile flow in rats or dogs. Choleresis induced by
these compounds occurs immediately after acute admin-
istration and is predominantly due to the osmotic activity
of the compound and/or its metabolites. However, the
 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
t istration 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 μ of the compound and/or its metabolites. However, the volume excreted per microequivalent of chemical exceeds
the theoretical maximal increment in bile flow $(7 \mu l, \mu$ mol) anticipated for most of the above xenobiotics
(die volume excreted per microequivalent of chemical exceeds
the theoretical maximal increment in bile flow $(7 \mu)/$
 $(\mu$ mol) anticipated for most of the above xenobiotics
(diethyl maleate, 13 μ l in rat and 17 μ l in dog; the theoretical maximal increment in bile flow $(7 \mu l/\mu \text{mol})$ anticipated for most of the above xenobiotics (diethyl maleate, $13 \mu l$ in rat and $17 \mu l$ in dog; iodipamide, iodoxamate, and ioglycamide, $22 \mu l$; valproic a (diethyl maleate, 13 μ l in rat and 17 μ l in dog; iodipamide, 7 to 14 μ l/ μ mol, respectively (71, 493, 1080). Apparently, ulated. 7 to 14 μ l/ μ mol, respectively (71, 493, 1080). Apparently,
other determinants of canalicular secretion are also stim-
ulated.
Other substances that induce choleresis by stimulating
bile acid-independent flow include

Other substances that induce choleresis by stimulating
bile acid-independent flow include theophylline and other determinants of canalicular secretion are also stim-
ulated.
Other substances that induce choleresis by stimulating
bile acid-independent flow include theophylline and
cAMP (70), hydrocortisone (276, 759), thyroxine Downloaded from pharmrev.aspetjournals.org at Thammasart University on December 8, 2012

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glucagon (70), and possibly vasopressin (941). The hy-
polipidemic drug, nafenopin, increases liver weight (382) KLAASSEN ANI
glucagon (70), and possibly vasopressin (941). The hy-
polipidemic drug, nafenopin, increases liver weight (382)
and promotes a profound choleresis in rats (732) al-KLAASSEN Alglucagon (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 comple glucagon (70), and possibly vasopressin (941). The hypolipidemic drug, nafenopin, increases liver weight (382) cand promotes a profound choleresis in rats (732) altitled though the mechanism for choleresis is not completel 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 unders polipidemic drug, nafenopin, increases liver weight (382) can
and promotes a profound choleresis in rats (732) al-
though the mechanism for choleresis is not completely suc
understood. In addition, dihydroxydibutyl ether i and promotes a profound choleresis in rats (732) al-
though the mechanism for choleresis is not completely
sunderstood. In addition, dihydroxydibutyl ether in-
creases canalicular bile flow without affecting bile acid
in e though the mechanism for choleresis is not completely suce understood. In addition, dihydroxydibutyl ether in-
creases canalicular bile flow without affecting bile acid inti-
excretion (215). Administration of non-toxic d understood. In addition, dihydroxydibutyl ether in-
creases canalicular bile flow without affecting bile acid int
excretion (215). Administration of non-toxic doses of fun
perhexiline maleate stimulates bile flow and bile creases canalicular bile flow without affecting bile acid in
excretion (215). Administration of non-toxic doses of fur-
perhexiline maleate stimulates bile flow and bile acid les
excretion but inhibits BSP transport maxim excretion (215). Administration of non-toxic doses
perhexiline maleate stimulates bile flow and bile a
excretion but inhibits BSP transport maximum (T_m) a
its choleretic effect (494). Tienilic acid is choleretic wh
admi perhexiline maleate stimulates bile flow and bile accertion but inhibits BSP transport maximum (T_m) and its choleretic effect (494). Tienilic acid is choleretic whe administered intravenously and does not undergo enterne excretion but inhibits BSP transport maximum (T_m) a
its choleretic effect (494). Tienilic acid is choleretic wh
administered intravenously and does not undergo enter-
hepatic circulation (736). Bucolome, a non-steroid
an its choleretic effect (494). Tienilic acid is choleretic when
administered intravenously and does not undergo entero-
hepatic circulation (736). Bucolome, a non-steroidal,
anti-inflammatory drug, produces a pronounced cho administered intravenously and does not undergo entero-
hepatic circulation (736). Bucolome, a non-steroidal, canti-inflammatory drug, produces a pronounced choler-
esis without increasing bile acid excretion (617, 618). hepatic circulation (736). Bucolome, a non-steroidal, contri-inflammatory drug, produces a pronounced choleresis without increasing bile acid excretion (617, 618). contribution of the osmotic properties of the drug as onl anti-inflammatory drug, produces a pronounced choleresis without increasing bile acid excretion (617, 618). Conclude Although 27 μ of bile are excreted per micromole of m bucolome, the choleresis may not be due to the esis withou
Although 2
bucolome,
properties
into bile.
3. Micro though 27 μ l of bile are excreted per micromole of microlome, the choleresis may not be due to the osmotic Interpreties of the drug as only small amounts are excreted mate to bile.
3. *Microsomal Enzyme Inducers*. Phen

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 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 into bile.

3. Microsomal Enzyme Inducers. Phenobarbital ansome other barbiturates enhance bile flow and the biliar

clearance of drugs and endogenous metabolites (159, 620

621, 663, 992). The time course of bile flow enh 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 some other barbiturates enhance bile flow and the biliary
clearance of drugs and endogenous metabolites (159, 620, wil
621, 663, 992). The time course of bile flow enhancement
for
does not correlate with increased liver we 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 micro-
somal enzyme activity, and other enzyme inducers s 621, 663, 992). The time course of bile flow enhancement
does not correlate with increased liver weight or micro-
isomal enzyme activity, and other enzyme inducers such
as 3-methylcholanthrene fail to stimulate bile produ does not correlate with increased liver weight or micro-
somal enzyme activity, and other enzyme inducers such
as 3-methylcholanthrene fail to stimulate bile production
 $(619, 640)$. Phenobarbital apparently stimulates bi 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-independen as 3-methylcholanthrene fail to stimulate bile production $1.$ (619, 640). Phenobarbital apparently stimulates bile effection acid-independent flow in the rat (102, 622, 900) and been rhesus monkey (962). This increase in (619, 640). Phenobarbital apparently stimulates bile
acid-independent flow in the rat $(102, 622, 900)$ and b
rhesus monkey (962). This increase in bile acid-inde-
pendent flow might be mediated through an increase in
Na acid-independent flow in the rat $(102, 622, 900)$ and
rhesus monkey (962). This increase in bile acid-inde-
pendent flow might be mediated through an increase in
Na⁺-K⁺-ATPase (968, 1091). Other microsomal enzyme
ind rhesus monkey (962). This increase in bile acid-inde-
pendent flow might be mediated through an increase in
Na⁺-K⁺-ATPase (968, 1091). Other microsomal enzyme
inducers that are choleretic include carbutamide (1198),
d pendent 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-16 α -carbonitrile (PCN), Na⁺-K⁺-ATPase (968, 1091). Other microsomal enzym
inducers that are choleretic include carbutamide (1198)
diazepam (459), pregnenolone-16 α -carbonitrile (PCN)
and spironolactone (1110, 1300). The enzyme induce
and h inducers that are choleretic include carbutamide (1198
diazepam (459), pregnenolone-16 α -carbonitrile (PCN
and spironolactone (1110, 1300). The enzyme induc
and hypolipidemic agent clofibrate stimulates bile aci
indepen diazepam (4
and spirono
and hypolipin
independent
tion (697).
B. Cholestas and sphonolacu
and hypolipiden
independent flov
tion (697).
B. Cholestasis
Cholestasis is

enviously and tion (697).

B. Cholestasis taured by increased levels of biliary substances in the blood. Common bile duct stones, sclerosing cholangitis, substances in B. Cholestasis
Cholestasis is bile flow stagnation which is usually
accompanied by increased levels of biliary substances ir
blood. Common bile duct stones, sclerosing cholangitis
or cancer of the biliary tree or the pancr B. 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 obs Cholestasis is bile flow stagnation which is usu
accompanied by increased levels of biliary substance
blood. Common bile duct stones, sclerosing cholang
or cancer of the biliary tree or the pancreas can obstr
bile flow and accompanied by increased levels of biliary substances
blood. Common bile duct stones, sclerosing cholangii
or cancer of the biliary tree or the pancreas can obstru
bile flow and produce extrahepatic cholestasis. Intral
ula blood. Common bile duct stones, sclerosing cholangitis, surface or cancer of the biliary tree or the pancreas can obstruct cholestasis (2holestasis cholestasis C244). In matory processes, can also cause cholestasis (244). or cancer of the biliary tree or the pancreas can obstruct
bile flow and produce extrahepatic cholestasis. Intralob-
ular obstruction, which occurs during cirrhosis or inflam-
matory processes, can also cause cholestasis (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 a matory 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 derangem matory processes, can also cause cholestasis (244). In notion contrast, drug-induced "intrahepatic cholestasis" is ap-
parently due to biochemical interference with cellular choles
function (1298). This term emphasizes fun contrast, drug-induced "intrahepatic cholestasis" is apparently due to biochemical interference with cellular
function (1298). This term emphasizes functional de-
rangement of the hepatocanalicular bile secretory system
an parently due to biochemical interference with cellus function (1298). This term emphasizes functional rangement of the hepatocanalicular bile secretory system attempts to differentiate it from other mechanisthat could acco function (1298). This term emphasizes functional de-
rangement of the hepatocanalicular bile secretory system
and attempts to differentiate it from other mechanisms
that could account for accumulation of biliary constitu-
 rangement of the hepatocanalicular bile secretory system
and attempts to differentiate it from other mechanisms
that could account for accumulation of biliary constitu-
ents in plasma and clinical jaundice. Intrahepatic ch and attempts to differentiate it from c
that could account for accumulation of
ents in plasma and clinical jaundice.
lestasis has been reviewed extensively
927, 931, 932, 972, 1028, 1054, 1298).
Our present understanding o at could account for accumulation of biliary constits
is in plasma and clinical jaundice. Intrahepatic cl
tasis has been reviewed extensively (85, 101, 384, 5
7, 931, 932, 972, 1028, 1054, 1298).
Our present understanding ents in plasma and clinical jaundice. Intrahepatic clestasis has been reviewed extensively (85, 101, 384, 5927, 931, 932, 972, 1028, 1054, 1298).
Our present understanding of the pathogenic mechanisms involved in chemical-

lestasis 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 l

D WATKINS
cally and functionally similar to those observed clinically,
can be induced by chemicals in laboratory animals. How-D WATKINS
cally and functionally similar to those observed clinicall
can be induced by chemicals in laboratory animals. How
ever, no experimental model of cholestasis has bee D WATKINS
cally and functionally similar to those observed clinically,
can be induced by chemicals in laboratory animals. How-
ever, no experimental model of cholestasis has been
successfully developed which duplicates all cally and functionally similar to those observed clinica
can be induced by chemicals in laboratory animals. Hever, no experimental model of cholestasis has b
successfully developed which duplicates all the manifestions obs cally and functionally similar to those observed clinically
can be induced by chemicals in laboratory animals. How
ever, no experimental model of cholestasis has bees
successfully developed which duplicates all the manifes 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 intra ever, no experimental model of cholestasis has been
successfully developed which duplicates all the manifes-
tations observed in man. Investigations on experimental
intrahepatic cholestasis suggest that several different
f 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 cho tations observed in man. Investigations on experimenta
intrahepatic cholestasis suggest that several differen
functional alterations may be important. Targets of cho
lestatic chemicals may be the lipid phase of several cel 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. Int 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. Int lestatic chemicals may be the lipid phase of several cell
structures: the sinusoidal and/or canalicular membranes,
the endoplasmic reticulum, and the mitochondria. Inter-
actions with lipids or proteins within these membra structures: the sinusoidal and/or canalicular membrane
the endoplasmic reticulum, and the mitochondria. Inte
actions with lipids or proteins within these membrane
can impair cellular functions such as the activity
carrier the endoplasmic reticulum, and the mitochondria. In actions with lipids or proteins within these membra
can impair cellular functions such as the activity
carrier proteins or microsomal enzymes and the interestively reflul actions with lipids or proteins within these membran
can impair cellular functions such as the activity
carrier proteins or microsomal enzymes and the intr
cellular energy supply. Other targets could be cytopla
mic binding can impair cellular functions such as the activity of carrier proteins or microsomal enzymes and the intra-
cellular energy supply. Other targets could be cytoplas-
mic binding proteins and possibly the microfilaments.
Int carrier proteins or microsomal enzymes and the intra-
cellular energy supply. Other targets could be cytoplas-
mic binding proteins and possibly the microfilaments.
Interference with other regulatory processes in the cell
 cellular 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
dru 1054). terference with other regulatory processes in the cell
ay also be important. However, the primary event of
ug-induced intrahepatic cholestasis is unknown (932,
54).
Several chemicals that have been extensively studied
Il b

may also be important. However, the primary event of drug-induced intrahepatic cholestasis is unknown (932, 1054).
1054).
Several chemicals that have been extensively studied will be discussed to facilitate our understandi drug-induced intrahepatic cholestasis is unknown (932, 1054).
1054).
Several chemicals that have been extensively studied
will be discussed to facilitate our understanding of bile
formation and biliary excretion. A more co 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 chemicals that have been exter-
will be discussed to facilitate our unders-
formation and biliary excretion. A more-
listing of cholestatic agents may be obtaine
reviews (669, 905, 928, 931, 1297, 1298).
I. Endoge Il be discussed to facilitate our understanding of bile
 1. Enation and biliary excretion. A more comprehensive
 ing of cholestatic agents may be obtained from several
 1. Endogenous Compounds. a. BILE ACIDS. The tox

independent flow and decreases biliary cholesterol excre-

environment to a high Na⁺/low K⁺ biliary environment

could result in intracanalicular precipitation of sodium

B. Cholestasis

cholestasis is bile flow stagn 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 listing of cholestatic agents may be obtained from severa
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 sinc 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 reac-

tion in rabbi 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 Jav effects of the monohydroxy bile salt, lithocholate, have
been known since Holsti described a ductular cell reac-
tion in rabbits fed desiccated hog bile (503, 504). Later
Javitt (554) reported rapid onset of cholestasis in 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. tion in rabbits fed desiccated hog bile (503, 504). Lat
Javitt (554) reported rapid onset of cholestasis in ra
after intravenous infusion of taurolithocholic acid. O
hypothesis for this toxic response stated that aqueo
sol Javitt (554) reported rapid onset of cholestasis in rafter intravenous infusion of taurolithocholic acid. O
hypothesis for this toxic response stated that aqueo
solubility of sodium salts of lithocholate and its conj
gates after intravenous infusion of taurolithocholic acid. One
hypothesis for this toxic response stated that aqueous
solubility of sodium salts of lithocholate and its conju-
gates is lower than that of potassium salts (1099). solubility of sodium salts of lithocholate and its conjugates is lower than that of potassium salts (1099). Secresolubility 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 e gates 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 environment to a high $Na⁺/low K⁺$ biliary environment could result in intracanalicular precipitation of sodium 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 solub taurolithocholate (557, 1099). Abolition of cholestasis by
simultaneous infusion of primary bile acids is consistent
with this hypothesis (557, 944). The more soluble $3-\alpha$ -
sulfates of tauro- and glycolithocholate are le simultaneous infusion of primary bile acids is consistent
with this hypothesis (557, 944). The more soluble $3-\alpha$ -
sulfates of tauro- and glycolithocholate are less potent
cholestatic agents (346), a response that does no 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 excre 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 suppor mic 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, 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 trihy these metabolites (740). Additional studies support the notion that formation of insoluble salts in the hepatocy or the canalicular lumen may initiate hepatic injury are cholestasis (163). Administration of di- and trihydr notion that formatio
or the canalicular lu
cholestasis (163). At
bile acids prevents o
lestasis (576, 718).
More recent studi

lestasis (576, 718).
More recent studies indicate lithocholic acid directly
affects the structure, composition, and function of the cholestasis (163). Administration of di- and trihydroxy
bile acids prevents or reverses lithocholate-induced cho-
lestasis (576, 718).
More recent studies indicate lithocholic acid directly
affects the structure, compositi bile acids prevents or reverses lithocholate-induced cho-
lestasis (576, 718).
More recent studies indicate lithocholic acid directly
affects the structure, composition, and function of the
canalicular membrane (575-577, 7 lestasis (576, 718).
More recent studies indicate lithocholic acid direct
affects the structure, composition, and function of the
canalicular membrane (575–577, 718, 813). Na⁺-K
ATPase activity is decreased in hepatocyte 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 mem-
b 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 tr 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 indu 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 inhib

BILE FORMATION, HEPATIC UPTAKE, AND BILIARY EXCRETION 13 BILE FORMATION, HEPATIC UPTAKE, AND BILIARY EXCRETION
enzyme or decreased membrane fluidity. Significant or prevent depression of bile is
quantities of free cholesterol are released into the cana- droxy cholanic acid cause BILE FORMATION, HEPATIC
enzyme or decreased membrane fluidity. Significan
quantities of free cholesterol are released into the cana-
liculi from its limiting membrane within minutes of a BILE FORMATION, HEPATIC UPTAKE,
enzyme or decreased membrane fluidity. Significant or p
quantities of free cholesterol are released into the cana-
liculi from its limiting membrane within minutes of an
intravenous injectio enzyme or decreased membrane fluidity. Significant of quantities of free cholesterol are released into the cana-
liculi from its limiting membrane within minutes of an pintravenous injection of taurolithocholate (122). Thi enzyme or decreased membrane fluidity. Significant or
quantities of free cholesterol are released into the cana-
liculi from its limiting membrane within minutes of an
intravenous injection of taurolithocholate (122). This quantities of free cholesterol are released into the calculi from its limiting membrane within minutes of intravenous injection of taurolithocholate (122). The drastic change in membrane composition could moderative and pa liculi from its limiting membrane within minutes of an paint
ravenous injection of taurolithocholate (122). This calculation change in membrane composition could modify po
active and passive transport properties of the hep intravenous injection of taurolithocholate (122). This drastic change in membrane composition could modify lactive and passive transport properties of the hepatocytes and induce cholestasis. Recent preliminary data indicat drastic change in membrane composition could modify
active and passive transport properties of the hepato-
cytes and induce cholestasis. Recent preliminary data
indicate that inhibitors of protein synthesis apparently
bloc active and passive transport properties of the hepatotytes and induce cholestasis. Recent preliminary data oridicate that inhibitors of protein synthesis apparently polock the cholestatic response to lithocholic acid, sugg or prevent depression of bile flow; and c) allo-monohy-

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 (129

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 con-
jugate, appears in bile soon after administration and do

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 aci

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 f 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 f

indicator of the structural integrity of the plasmalem
is altered following administration of bile acid (8
Hyperpolarization was observed after treatment v
taurolithocholate at doses that decrease bile flow
hepatobiliary p

Hyperpolarization was observed after treatment with
taurolithocholate at doses that decrease bile flow and
hepatobiliary permeability (874). In contrast, taurocho-
late produces slight depolarization and increases in bile
 taurolithocholate at doses that decrease bile flow and
hepatobiliary permeability (874). In contrast, taurocho-
late produces slight depolarization and increases in bile
flow and permeability. However, lack of understandin 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
p 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. of the mechanisms which maintain the resting membrane
potential in hepatocytes makes accurate interpretation
of these data difficult.
Intrabiliary pressure generated during retrograde in-
trabiliary infusion of saline was

potential in hepatocytes makes accurate interpretation
of these data difficult.
Intrabiliary pressure generated during retrograde in-
trabiliary infusion of saline was increased while bile flow
decreased after intravenous of these data difficult.

Intrabiliary pressure generated during retrograde is

trabiliary infusion of saline was increased while bile flo

decreased after intravenous infusion of taurocholate or glyco-

(552). Simultaneou Intrabiliary pressure generated during retrograde in-
trabiliary infusion of saline was increased while bile flow
decreased after intravenous infusion of taurolithocholate
(552). Simultaneous infusion of taurocholate or gl

trabiliary 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 bil

cholestatic potency of three bile acids as taurodeoxycholate $>$ taurocholate when infused into rats. Bile acid overload appears to lead directly to cholestasis. Administration of tauroursodeoxycholate prevented taurochol fused into rats. Bile acid overload appears to lead directly

fused into rats. Bile acid overload appears to lead directly
to cholestasis. Administration of tauroursodeoxycholate
prevented taurocholate-induced cholestasis (612). Addi-
tional studies indicate the allo-monohydroxy bil to cholestasis. Administration of tauroursodeoxycholate
prevented taurocholate-induced cholestasis (612). Addi-
tional studies indicate the allo-monohydroxy bile acids
are cholestatic in rats (1215) and that a) $3-\beta$ -hydr

the cause, of more fundamental alterations of bil
mation and hepatocyte morphology.
Bile acids other than lithocholic acid and its conju
are also cholestatic. Drew and Priestly (264) ranke
cholestatic potency of three bile mation 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 taurodeoxycho-

late > taur

is acids decreased intrabiliary pressure. These changes
intrabiliary pressure were likely the result, and not
e cause, of more fundamental alterations of bile for-
ation and hepatocyte morphology.
Bile acids other than lit

trabiliary pressure and cholestasis,
bile acids decreased intrabiliary pre
in intrabiliary pressure were likely
the cause, of more fundamental al
mation and hepatocyte morphology
Bile acids other than lithocholic a

produced membrane-bound cytoplasmic vacuolas 10 min after injection while appearance of acid in bile was delayed. Thus, sulfated glycolacid is cholestatic in rats by a mechanism a different from that of lithocholic acid (1

cytes and induce cholestasis. Recent preliminary data ochindicate that inhibitors of protein synthesis apparently pot block the cholestatic response to lithocholic acid, suggesting that the microsomes may be potentially in indicate that inhibitors of protein synthesis apparently polock the cholestatic response to lithocholic acid, sug-
gesting that the microsomes may be potentially involved blin mediating the cholestasis (1293). Studies in r 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 gesting 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 d 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-sulfat little effect on bile flow; lithocholate-sulfate depresses to
bile flow by 20% while glycolithocholate-sulfate reduces cl
bile flow by 60% in a dose-dependent manner (1292). d
Lithocholate-sulfate, mainly excreted as the t bile flow by 60% in a dose-dependent manner (1292). d
Lithocholate-sulfate, mainly excreted as the taurine con-
jugate, appears in bile soon after administration and does
not produce morphological changes as evaluated by e KE, AND BILIARY EXCRETION 13
or prevent depression of bile flow; and c) allo-monohy-
droxy cholanic acid causes dilatation of canaliculi with
partial or total loss of microvilli and formation of peri-I:

or prevent depression of bile flow; and c) allo-monohy

droxy cholanic acid causes dilatation of canaliculi with

partial or total loss of microvilli and formation of peri

canalicular diverticuli. A recent report sugg or prevent depression of bile flow; and c) allo-monohy-
droxy cholanic acid causes dilatation of canaliculi with
partial or total loss of microvilli and formation of peri-
canalicular diverticuli. A recent report suggests or prevent depression of bile flow; and c) allo-monohy-
droxy cholanic acid causes dilatation of canaliculi with
partial or total loss of microvilli and formation of peri-
canalicular diverticuli. A recent report suggests droxy cholanic acid causes dilatation of canaliculi v
partial or total loss of microvilli and formation of p
canalicular diverticuli. A recent report suggests that
potency of dihydrotestosterone glucuronide is gre
than the 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 tauro canalicular diverticuli. A recent report suggests that the potency of dihydrotestosterone glucuronide is greater than the allo bile acids which is greater than taurolith-ocholate in producing cholestasis (818). The order o potency of dihydrotestosterone glucuronide is greathan the allo bile acids which is greater than tauroli ocholate in producing cholestasis (818). The order potency of bile acids to produce hemolysis (892) is simite to thei than the allo bile acids which is greater than taurolith-
ocholate in producing cholestasis (818). The order of
potency of bile acids to produce hemolysis (892) is similar
to their cholestatic potential. The reproducible, ocholate in producing cholestasis (818). The order of
potency of bile acids to produce hemolysis (892) is similar
to their cholestatic potential. The reproducible, reversi-
ble cholestatic response induced in rats by intra potency of bile acids to produce hemolysis (892) is similar
to their cholestatic potential. The reproducible, reversi-
ble cholestatic response induced in rats by intravenous
bile acid administration may be useful in study to their cholestatic potential. The reproducible, reversi-
ble cholestatic response induced in rats by intravenous
bile acid administration may be useful in studying the
characteristics of intrahepatic cholestasis. However ble cholestatic response induced in rats by intravenous
bile acid administration may be useful in studying the
characteristics of intrahepatic cholestasis. However, at
tempts to modify this response by drugs that produce
c 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 no characteristics of intrahepatic cholestasis. Howev
tempts to modify this response by drugs that picholestasis in man (chlorpromazine and erythror
do not appear to provide a suitable toxicological app
to prediction of their mpts to modify this response by drugs that produce
olestasis in man (chlorpromazine and erythromycin)
not appear to provide a suitable toxicological approach
prediction of their cholestatic potential (265).
b. MANGANESE-BI

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 sulfa iugate, appears in bile soon after administration and does
not produce morphological changes as evaluated by elec-
tron microscopy. In contrast, glycolithocholate sulfate
noroduced membrane-bound cytoplasmic vacuoles as ea tron microscopy. In contrast, glycolithocholate sulfate in produced membrane-bound cytoplasmic vacuoles as early in the appearance of the bile is a mechanism apparently acid in bile was delayed. Thus, sulfated glycolithoch 10 min after injection while appearance of the bile pro-
id in bile was delayed. Thus, sulfated glycolithocholic tati-
id is cholestatic in rats by a mechanism apparently dep-
fferent from that of lithocholic acid (1292). different from that of lithocholic acid (1292). tion
The transmembrane potential of the hepatocyte, an
indicator of the structural integrity of the plasmalemma, ani
is altered following administration of bile acid (874). i The transmembrane potential of the hepatocyte, an were indicator of the structural integrity of the plasmalemma, ani
is altered following administration of bile acid (874). ital
Hyperpolarization was observed after treatme is altered following administration of bile acid (874). its
Hyperpolarization was observed after treatment with wh
taurolithocholate at doses that decrease bile flow and ma
hepatobiliary permeability (874). In contrast, ta cholestasis in man (chlorpromazine and erythromyc
do not appear to provide a suitable toxicological approto
to prediction of their cholestatic potential (265).
b. MANGANESE-BILIRUBIN. Early studies by Witzlel
and colleague 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 intrave-
nous to prediction of their cholestatic potential (265).
b. MANGANESE-BILIRUBIN. Early studies by Witzleben
and colleagues (1274–1277) indicate that acute intrave-
nous administration of manganese sulfate reduces bile
flow and and colleagues $(1274-1277)$ indicate that acute intrave-
nous administration of manganese sulfate reduces bile
flow and the Tm for bilirubin excretion into bile, and
produces ultrastructural changes resembling the choles and colleagues (1274–1277) indicate that acute intrave
nous administration of manganese sulfate reduces bil
flow and the Tm for bilirubin excretion into bile, an
produces ultrastructural changes resembling the choles
tatic nous administration of manganese sulfate reduces bil
flow and the Tm for bilirubin excretion into bile, an
produces ultrastructural changes resembling the choles
tatic response. Bile flow was further reduced in a dose
depe flow and the Tm for bilirubin excretion into bile, and
produces ultrastructural changes resembling the choles-
tatic response. Bile flow was further reduced in a dose-
dependent manner after injection of bilirubin. In addi produces ultrastructural changes resembling the chole
tatic response. Bile flow was further reduced in a dos
dependent manner after injection of bilirubin. In add
tion, the manganese-induced ultrastructural chang
were exac tatic response. Bile flow was further reduced in a do-
dependent manner after injection of bilirubin. In ad-
tion, the manganese-induced ultrastructural chang-
were exacerbated by bilirubin and the cholestatic me-
anism wa 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 tion, the manganese-induced ultrastructural changes
were exacerbated by bilirubin and the cholestatic mech-
anism was postulated to involve intracanalicular precip-
itation of a manganese-bilirubin complex. However,
when B were exacerbated by bilirubin and the cholestatic mech-
anism was postulated to involve intracanalicular precip-
itation of a manganese-bilirubin complex. However,
when BSP was infused into the animals to prevent the
manga anism 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 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 when BSP was infused into the animals to prevent the
manganese-bilirubin cholestasis, biliary excretion of
manganese was significantly increased. Hence, the con-
centration of manganese in bile may not be a determining
fac manganese-bilirubin cholestasis, biliary excretion
manganese was significantly increased. Hence, the co
centration of manganese in bile may not be a determini
factor but the interaction between manganese and bi
rubin at th tant. factor but the interaction between manganese and bili-
rubin at the level of the hepatocyte may be more impor-
tant.
Use of the manganese-bilirubin-induced cholestasis as

of the mechanisms which maintain the resting membrane rubin approaches interpretation tant.

of these data difficult. Use

Intrabiliary pressure generated during retrograde in-

an experimental flow Combine

trabiliary inf trabiliary infusion of saline was increased while bile flow
decreased after intravenous infusion of taurolithocholate
(552). Simultaneous infusion of taurocholate or glyco-
cholate with taurolithocholate prevented the rise decreased after intravenous infusion of taurolithocholate (552). Simultaneous infusion of taurocholate or glyco-cholate with taurolithocholate prevented the rise in intrabiliary pressure and cholestasis, while the choleret (552). Simultaneous infusion of taurocholate or glyco-cholate with taurolithocholate prevented the rise in in-
trabiliary pressure and cholestasis, while the choleretic
bile acids decreased intrabiliary pressure. These cha in intrabiliary pressure were likely the result, and not net
the cause, of more fundamental alterations of bile for-
mation and hepatocyte morphology. an
Bile acids other than lithocholic acid and its conjugates ten
are al 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 taurodeoxycho-
chate > taurochenodeoxycholate > taurocholate whe late > taurochenodeoxycholate > taurocholate when in-
fused into rats. Bile acid overload appears to lead directly
to cholestasis. Administration of tauroursodeoxycholate
prevented taurocholate-induced cholestasis (612). prevented taurocholate-induced cholestasis (612). Additional studies indicate the allo-monohydroxy bile acids gare cholestatic in rats (1215) and that a) 3- β -hydroxy-5-lic α -cholanic acid (allo analog) is a more pot rubin 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 rubin 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 tant.
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
 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 bil 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
sequen 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
fo and bilirubin produces a rapid and reversible reduct
in bile flow if the substances are injected in pro
sequence and time interval (634), i.e. manganese f
followed by bilirubin 15 minutes later. Recently,
Lamirande and Pla 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-buta-
nediol sequence and time interval (634), i.e. manganese followed by bilirubin 15 minutes later. Recently, Lamirande and Plaa (239) demonstrated that 1,3-b
nediol, a potentiator of haloalkane hepatotoxicity (4
exacerbated mangane followed by bilirubin 15 minutes later. Recently, de-
Lamirande and Plaa (239) demonstrated that 1,3-buta-
nediol, a potentiator of haloalkane hepatotoxicity (480),
exacerbated manganese-bilirubin-, taurolithocholate-,
an Lamirande and Plaa (239) demonstrated that 1,3-buta-
nediol, a potentiator of haloalkane hepatotoxicity (480),
exacerbated manganese-bilirubin-, taurolithocholate-,
and α -naphthylisothiocyanate-induced cholestasis. Ponediol, a potentiator of haloalkane hepatotoxicity (480),
exacerbated manganese-bilirubin-, taurolithocholate-,
and α -naphthylisothiocyanate-induced cholestasis. Po-
tentiation of manganese-bilirubin cholestasis could exacerbated manganese-bilirubin-, taurolithochola
and α -naphthylisothiocyanate-induced cholestasis.
tentiation of manganese-bilirubin cholestasis could oc
by enhancement of biotransformation leading to
creased bilirubi and α -naphthylisothiocyanate-induced cholestasis. Potentiation of manganese-bilirubin cholestasis could occur
by enhancement of biotransformation leading to in-
creased bilirubin availability and/or increased susceptitentiation of manganese-bilirubin cholestasis could occur
by enhancement of biotransformation leading to in-
creased bilirubin availability and/or increased suscepti-
bility of cellular constituents to maganese. A recent creased bilirubin availability and/or increased suscepti-
bility of cellular constituents to maganese. A recent
report notes a marked modification in the amount of bile
canalicular membranes obtained by differential centri creased bilirubin availability and/or increased suscepti-
bility of cellular constituents to maganese. A recent
report notes a marked modification in the amount of bile
canalicular membranes obtained by differential centri bility of cellular constituents to maganese. A recent
report notes a marked modification in the amount of bile
canalicular membranes obtained by differential centrif-
ugation after manganese-bilirubin. These authors sug-
g canalicular membranes obtained by differential centrif-
ugation after manganese-bilirubin. These authors sug-
gest that manganese induces changes in the membrane
lipid layer that permits bilirubin incorporation and sub-
se canalicular membranes obt
ugation after manganese-b
gest that manganese induc
lipid layer that permits bili
sequent cholestasis (240).
2. Drugs. a. STEROIDS. Franklin after manganese-bilirubin. These authors sug-

2. Hat manganese induces changes in the membrane

id layer that permits bilirubin incorporation and sub-

puent cholestasis (240).

2. *Drugs.* a. STEROIDS. Cholestas

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EXELAASSEN AND W
bolic and contraceptive steroids has been observed in A
humans and laboratory animals (928). In humans, estra- indi KLAASSEN
humans and contraceptive steroids has been observed
humans and laboratory animals (928). In humans, estra-
diol, estriol, and oral contraceptives provoke a reversib KLAASSEN ANI

bolic and contraceptive steroids has been observed in

humans and laboratory animals (928). In humans, estra-

diol, estriol, and oral contraceptives provoke a reversible

retention of BSP and an increase in bolic and contraceptive steroids has been observed in
humans and laboratory animals (928). In humans, estra-
diol, estriol, and oral contraceptives provoke a reversible
retention of BSP and an increase in plasma alkaline
p bolic and contraceptive steroids has been observed in A
humans and laboratory animals (928). In humans, estra-
indiol, estriol, and oral contraceptives provoke a reversible velocate
retention of BSP and an increase in plas humans and laboratory animals (928). In humans, estra-
diol, estriol, and oral contraceptives provoke a reversible
retention of BSP and an increase in plasma alkaline sig
phosphatase activity (679, 683, 861). Estrone produ diol, estriol, and oral contraceptives provoke a reversil
retention of BSP and an increase in plasma alkali
phosphatase activity (679, 683, 861). Estrone produce
30% reduction of bile flow in female rats during both t
basa phosphatase activity (679, 683, 861). Estrone produces 30% reduction of bile flow in female rats during both th
basal period and during dehydrocholate-induced choles
esis (352). Rats given ethinylestradiol for 5 days devel 30% reduction of bile flow in female rats during both the the basal period and during dehydrocholate-induced choler-
esis (352). Rats given ethinylestradiol for 5 days develop (
hepatomegaly and depression of both basal an basal period and during dehydrocholate-induced choler-
esis (352). Rats given ethinylestradiol for 5 days develop (5
hepatomegaly and depression of both basal and BSP- ce
stimulated bile flow (492). Estrone causes a 50% de hepatomegaly and depression of both basal and BSP- ceptibility to steroid-induced cholestasis may be due to stimulated bile flow (492). Estrone causes a 50% decrease variations in inherent tissue sensitivity or in biotrans 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
fransport into bile. Similar effects have been observed
af 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-17 β d in steady-state BSP excretion by affecting its active for transport into bile. Similar effects have been observed after ethinylestradiol (446, 683). Estradiol-17 β decreased obile flow and the biliary excretion of diphe transport into bile. Similar effects have been observater ethinylestradiol (446, 683). Estradiol-17 β decreas bile flow and the biliary excretion of diphenylhydanto in perfused rat liver and in vivo (1220). Chronic estr in perfused rat liver and in vivo (1220). Chronic estrogen

Anabolic steroids such as methyltestosterone and noradministration reduced biliary excretion of BSP, biliru-
bin, and other organic anions in humans (203, 714, 821)
and rats (376, 474, 475).
Anabolic steroids such as methyltestosterone and nor-
ethandrolone produce dose-rel bin, and other organic anions in humans (203, 714, 821)
and rats (376, 474, 475).
Anabolic steroids such as methyltestosterone and nor-
ethandrolone produce dose-related increases in BSP re-
tention (472, 726, 1205). Norbo and rats (376, 474, 475). and rats (376, 474, 475).

Anabolic steroids such as methyltestosterone and nor-

ethandrolone produce dose-related increases in BSP re-

intention (472, 726, 1205). Norbolethone also impairs st
 Anabolic steroids such as methyltestosterone and nor-
ethandrolone produce dose-related increases in BSP re-
tention (472, 726, 1205). Norbolethone also impairs
clearance of BSP and indocyanine green in isolated
perfused r tention (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, estra-
diol, a tention (472, 726, 1205). Norbolethone also impairs straclearance of BSP and indocyanine green in isolated isol
perfused rat livers (79) and decreases bile flow in higher ery
concentrations. Furthermore, norethandrolone, e clearance of BSP and indo
perfused rat livers (79) and d
concentrations. Furthermore
diol, and progesterone inhibi
isolated hepatocytes (1055).
Estrogens inhibit bile flow concentrations. Furthermore, norethandrolone, estra-
diol, and progesterone inhibit taurocholate uptake into
isolated hepatocytes (1055).
Estrogens inhibit bile flow of both bile acid-dependent
(446, 805, 913) and -indepen

concentrations. Furthermore, norethandrolone, estra-
diol, and progesterone inhibit taurocholate uptake into
isolated hepatocytes (1055).
Estrogens inhibit bile flow of both bile acid-dependent
(446, 805, 913) and -indepen diol, and progesterone inhibit taurocholate uptake into
isolated hepatocytes (1055). ti
Estrogens inhibit bile flow of both bile acid-dependent th
(446, 805, 913) and -independent (446, 805) fractions. et
These effects may isolated hepatocytes (1055). it
Estrogens inhibit bile flow of both bile acid-dependent the
(446, 805, 913) and -independent (446, 805) fractions. eq
These effects may result from increased permeability of in
the biliary t Estrogens inhibit bile flow of both bile acid-dependent the $(446, 805, 913)$ and -independent $(446, 805)$ fractions. equid These effects may result from increased permeability of in curreliantly tree $(352, 913)$, incre (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
co 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
ar e biliary tree (352, 913), increased microviscosity of patocyte membranes (595, 1091), or a decrease in ncentration of Na⁺-K⁺-ATPase (233, 474, 968), but end due to an alteration in bile acid carriers (1090). Recent e

hepatocyte membranes (595, 1091), or a decrease in concentration of $Na^+ \cdot K^+ \cdot ATPase$ (233, 474, 968), but are not due to an alteration in bile acid carriers (1090).
Recent evidence indicates the D-ring glucuronide conjugat 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 f are not due to an alteration in bile acid carriers (1090).

Recent evidence indicates the D-ring glucuronide con-

jugate of estradiol is cholestatic in rats (804). In fact,

intravenous injection of several steroids conju Recent evidence indicates the D-ring glucuronide con-
jugate 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, jugate of estradiol is cholestatic in rats (804). In fact, c.
intravenous injection of several steroids conjugated with-
glucuronic acid on the D-ring, but not the A-ring, induces niec
an immediate, dose-related, reversibl intravenous injection of several ste
glucuronic acid on the D-ring, but i
an immediate, dose-related, reverithe cholestatic effect of several st
the glucuronide conjugate (805).
Administration of phenobarbite action of the D-ring, but not the A-ring, induces

immediate, dose-related, reversible cholestasis. Thus

an e cholestatic effect of several steroids might be due to

sule glucuronide conjugate (805).

Administration of ph

an immediate, dose-related, reversible cholestasis. Thus an the cholestatic effect of several steroids might be due to sulte glucuronide conjugate (805).

https://windinferaction of phenobarbital, which increases the is
 the cholestatic effect of several steroids might be due the glucuronide conjugate (805).

Administration of phenobarbital, which increases the acid-independent fraction of bile flow, reverses the ethinylestradiol-induced c 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 infu 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 eth-
 bile acid-independent fraction of bile flow, reverses the ethinylestradiol-induced cholestasis (440). Furthermore clearance of infused taurocholate was reduced in eth
inylestradiol-treated rats and was not reversed after p ethinylestradiol-induced cholestasis (440). Furthermore, of
clearance of infused taurocholate was reduced in eth-
inylestradiol-treated rats and was not reversed after ch
phenobarbital pretreatment (446, 1090). Triton WR-
 clearance of infused taurocholate was reduced in
inylestradiol-treated rats and was not reversed
phenobarbital pretreatment (446, 1090). Triton
1339, a nonionic detergent, has been shown to retur-
decreased membrane fluidi inylestradiol-treated rats and was not reversed after chomehobarbital pretreatment (446, 1090). Triton WR-
1339, a nonionic detergent, has been shown to return the and
decreased membrane fluidity produced by ethinylestra-
 phenobarbital pretreatment (446, 1090). Triton WR-
1339, a nonionic detergent, has been shown to return the
decreased membrane fluidity produced by ethinylestra-
diol toward normal and reestablish basal bile flow and
bile 1339, a nonionic detergent, has been shown to return the
decreased membrane fluidity produced by ethinylestra-
diol toward normal and reestablish basal bile flow and
bile acid excretion (1090). However, Hoenig (492) has
r decreased membrane fluidity produced by ethinylestra-
diol toward normal and reestablish basal bile flow and
bile acid excretion (1090). However, Hoenig (492) has
recently been unable to reproduce these protective effects
 diol toward normal and reestablish basal bile flow and
bile acid excretion (1090). However, Hoenig (492) has bile
recently been unable to reproduce these protective effects (3)
of Triton WR 1339 on ethinylestradiol-induced bile acid excretion (1090). However, Hoenig (492)
recently been unable to reproduce these protective eff
of Triton WR 1339 on ethinylestradiol-induced chan
Coadministration of S-adenosylmethionine has also b
shown to rever recently been unable to reproduce these protective effects (3
of Triton WR 1339 on ethinylestradiol-induced changes. he
Coadministration of S-adenosylmethionine has also been in
shown to reverse the cholestasis produced by Coadministration of S-adenosylmethionine has also been
shown to reverse the cholestasis produced by ethinyles-
tradiol, possibly by enhancing the biliary excretion of its
methylated metabolites (1143, 1144).

phosphatase activity (679, 683, 861). Estrone produces a man have been reported in some strains of mice (DS and 30% reduction of bile flow in female rats during both the C57BL, most sensitive; CBA and C3H, intermediate; an Although the results in laboratory animals may be D WATKINS
Although the results in laboratory animals may be
indicative of cholestasis, no demonstration of fully de-
veloped intrahepatic lesions has been made. However, D WATKINS
Although the results in laboratory animals may be
indicative of cholestasis, no demonstration of fully de-
veloped intrahepatic lesions has been made. However,
signs very similar to those of intrahepatic cholesta Although the results in laboratory animals may be
indicative of cholestasis, no demonstration of fully de-
veloped intrahepatic lesions has been made. However,
signs very similar to those of intrahepatic cholestasis in
man Although the results in laboratory animals may be
indicative of cholestasis, no demonstration of fully de-
veloped intrahepatic lesions has been made. However,
signs very similar to those of intrahepatic cholestasis in
man 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 veloped 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
I man have been reported in some strains of mice (DS and 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 suscept 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 va formation. ceptibility to steroid-induced cholestasis may be due to variations in inherent tissue sensitivity or in biotrans-
formation.
b. ERYTHROMYCINS. There are several clinical reports

bile flow and the biliary excretion of diphenylhydantoin lauryl sulfate salt of erythromycin propionate (138, 756).
in perfused rat liver and in vivo (1220). Chronic estrogen Other derivatives have a lower potential to pro ceptibility to steroid-induced cholestasis may be due to
variations in inherent tissue sensitivity or in biotrans-
formation.
b. ERYTHROMYCINS. There are several clinical reports
of mild reversible cholestasis associated w variations in inherent tissue sensitivity or in biotrans-
formation.
b. ERYTHROMYCINS. There are several clinical reports
of mild reversible cholestasis associated with use of the
lauryl sulfate salt of erythromycin propio formation.

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 potent 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 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 lestasis (184). Signs of a typical cholestatic reaction
include hyperbilirubinemia, elevation of serum aspartaminotransferase and alkaline phosphatase activiti
and fever. An erythromycin-induced cholestatic reaction
in exp 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 demon-
str aminotransferase and alkaline phosphatase activities,
and fever. An erythromycin-induced cholestatic reaction
in experimental animals in vivo has not been demon-
strated (928). However, reduction of bile flow in the
isolat and fever. An erythromycin-induced cholestatic reaction
in experimental animals in vivo has not been demon-
strated (928). However, reduction of bile flow in the
isolated rat liver has been observed after treatment with
er 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). I strated (928). However, reduction of bile flow in the isolated rat liver has been observed after treatment wivery
thromycin propionate and its lauryl sulfate salt (598).
Inability to demonstrate cholestasis in laboratory a isolated rat liver has been observed after treatment with
erythromycin propionate and its lauryl sulfate salt (598).
Inability to demonstrate cholestasis in laboratory ani-
mals may be related to species variation. Biliar Other derivatives have a lower potential to produce cho-
lestaatsi (184). Signs of a typical cholestatic reaction
include hyperbilirubinemia, elevation of serum aspartate
aminotransferase and alkaline phosphatase activiti Inability to demonstrate cholestasis in laboratory ani-
mals may be related to species variation. Biliary excre-
tion of erythromycin is the major route of elimination in
the rat, but the importance of this route in man is mals 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 tion of erythromycin is the major route of elimination i
the rat, but the importance of this route in man
equivocal (830, 831). The most cytotoxic erythromyci
in cultured Chang cells (hepatocytes) was the propionat
and rel 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 prop-
 equivocal (830, 831). The most cytotoxic erythromycin
in cultured Chang cells (hepatocytes) was the propionate
and relative cytotoxicity correlated with surfactant prop-
erties (272). A similar relationship between surfact in cultured Chang cells (hepatocytes) was the propionat
and relative cytotoxicity correlated with surfactant prop
erties (272). A similar relationship between surfactan
properties and cytotoxicity in in vitro preparations and relative cytotoxicity correlated with surfactant projecties (272). A similar relationship between surfactant properties and cytotoxicity in in vitro preparations hippen noted for bile acids, phenothiazines, and the lax

properties and cytotoxicity in in vitro preparations
been noted for bile acids, phenothiazines, and the la
tive dioctylsulfosuccinate (275).
c. PHENOTHIAZINES. Intravenous injection of ch
promazine reduces bile flow in dog been noted for bile acids, phenothiazines, and the laxative dioctylsulfosuccinate (275).

c. PHENOTHIAZINES. Intravenous injection of chlor-

promazine reduces bile flow in dogs which is accompa-

nied by an increase in bi tive dioctylsulfosuccinate (275).

c. PHENOTHIAZINES. Intravenous injection of chlor-

promazine reduces bile flow in dogs which is accompa-

nied by an increase in bilirubin concentration (1077) and

an increase in intrab c. PHENOTHIAZINES. Intravenous injection of c
promazine reduces bile flow in dogs which is accon-
initial by an increase in bilirubin concentration (1077)
an increase in intrabiliary pressure (1126). Simila
sults were obse promazine reduces bile flow in dogs which is accompa-
nied by an increase in bilirubin concentration (1077) and
an increase in intrabiliary pressure (1126). Similar re-
sults were observed in rats (673). Whether chlorproma nied by an increase in bilirubin concentration (1077) and
an increase in intrabiliary pressure (1126). Similar re-
sults were observed in rats (673). Whether chlorproma-
zine-induced neurohumoral changes could be responsi 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 m sults were observed in rats (673). Whether chlorproma-
zine-induced neurohumoral changes could be responsible
is unknown (1123). Chlorpromazine decreases bile flow
in monkeys (1003, 1149), which may be due to inhibition
of zine-induced neurohumoral changes could be responsities unknown (1123). Chlorpromazine decreases bile flum monkeys (1003, 1149), which may be due to inhibitiof Mg^{++} - or Na⁺-K⁺-ATPases (1023), and depresses t plasma 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
cho 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-induce
cholestasis is also characterized by a decrease in of Mg^{++} - or Na^+ -K⁺-ATPases (1023), and depresses t
plasma clearance of BSP (291). Chlorprothixene-induc
cholestasis is also characterized by a decrease in b
acid-independent flow which depresses the biliary cleance plasma clearance of BSP (291). Chlorprothixene-induced cholestasis is also characterized by a decrease in bilacid-independent flow which depresses the biliary clearance and Tm for BSP (2). Other neuroleptics, *cis*-thiothi cholestasis is also characterized by a decrease in bile
acid-independent flow which depresses the biliary clear-
ance and Tm for BSP (2). Other neuroleptics, *cis*-thi-
othixene and both *cis* and *trans* isomers of flupen acid-independent flow which depresses the biliary clear-
ance and Tm for BSP (2). Other neuroleptics, *cis*-thi-
othixene and both *cis* and *trans* isomers of flupenthixol
and clopenthixol, cause dose-dependent reductions ance and Tm for BSP (2). Other neuroleptics, *cis*-thi-
othixene and both *cis* and *trans* isomers of flupenthixol
and clopenthixol, cause dose-dependent reductions in
bile flow, and elimination of BSP and indocyanine gre othixene 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 effec 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
indi bile flow, and elimina
(3). Decreased anion
hepatic uptake or E
indicate depression o
unknown mechanism
Hepatotoxicity has). Decreased anion excretion is not due to an effect on patic uptake or BSP conjugation rate. These data dicate depression of bile acid-independent flow by an known mechanism.
Hepatotoxicity has been demonstrated in isolat indicate depression of bile acid-independent flow by an
unknown mechanism.
Hepatotoxicity has been demonstrated in isolated per-
fused rat liver as a reduction in bile flow and BSP

PHARMACOLOGICAL REVIEWS

BILE FORMATION, HEPAT
excretion after addition to the perfusate of chlorproxine (594, 599, 1000), other phenothiazines (1185), c BILE FORMATION, HEPATIC
excretion after addition to the perfusate of chlorprom
zine (594, 599, 1000), other phenothiazines (1185), chlo
diazepoxide, (5) or chlorprothixene (2). Dose-relate BILE FORMATION, HEPATIC UPT.
excretion after addition to the perfusate of chlorproma-
zine (594, 599, 1000), other phenothiazines (1185), chlor-
diazepoxide, (5) or chlorprothixene (2). Dose-related
leakage of intracellula excretion after addition to the perfusate of chlorpron
zine (594, 599, 1000), other phenothiazines (1185), chl
diazepoxide, (5) or chlorprothixene (2). Dose-relat
leakage of intracellular enzymes from isolated hepa
cytes i excretion after addition to the perfusate of chlorproma-
zine (594, 599, 1000), other phenothiazines (1185), chlor-
diazepoxide, (5) or chlorprothixene (2). Dose-related
leakage of intracellular enzymes from isolated hepat zine (594, 599, 1000), other phenothiazines (1185), chlor-
diazepoxide, (5) or chlorprothixene (2). Dose-related
leakage of intracellular enzymes from isolated hepato-
cytes is observed after exposure to phenothiazines (2, diazepoxide, (5) or chlorprothixene (2). Dose-related bileakage of intracellular enzymes from isolated hepato-
cytes is observed after exposure to phenothiazines (2, app
273), thioxanthenes (6), and tricyclic antidepressan 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 cytes is observed after exposure to phenothiazines (2, aperal), thioxanthenes (6), and tricyclic antidepressants (4). and Chlorpromazine also inhibits bile acid excretion when added to the perfusate in isolated liver of th 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, th added to the perfusate in isolated liver of the rat (1166). added to the perfusate in isolated liver of the rat (1166). needled to the perfusion is reduced, the inhibition of
taurocholate excretion by chlorpromazine is predomi-
nantly due to a generalized effect on the plasma mem-
 Although hepatic perfusion is reduced, the inhibition of taurocholate excretion by chlorpromazine is predomi-
nantly due to a generalized effect on the plasma mem-
branes of hepatocytes (1165). In fact, these in vitro el
r 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 sur nantly due to a generalized effect on the plasma mem-
branes of hepatocytes (1165). In fact, these in vitro elin
results may be manifestations of a direct toxic effect of gate
the surfactant properties of these drugs (274, 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 stasis. *3. Other Chemicals.* a. *α*-NAPHTHYLISOTHIOCYANATHTINI. A single dose of ANIT produces a dose-dependent cholostasis.

3. *Other Chemicals.* a. *α*-NAPHTHYLISOTHIOCYANATHTINI. A single dose of ANIT produces a dose-depende

major mechanism for production of intrahepatic chole-
stasis.
3. Other Chemicals. a. α -NAPHTHYLISOTHIOCYANATE
(ANIT). A single dose of ANIT produces a dose-dependent
cholestasis and hyperbilirubinemia in susceptible sp stasis.

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 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, on (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 2 cholestasis and hyperbilirubinemia in susceptible species chol
such as rat and mouse (83, 84, 535, 925). In the rat, onset chol
of hyperbilirubinemia occurs between 12 and 24 hours excr
and peaks at 5 days before returning such as rat and mouse (83, 84, 535, 925). In the rat, onset
of hyperbilirubinemia occurs between 12 and 24 hours ex
and peaks at 5 days before returning to normal values at fe
about 7 days. The decrease in bile flow is mor 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
ab 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 resista about 7 days. The decrease in bile flow is more abrupt in ordination of mice, occurring between 16 and 24 hours and lasting 7
about 5 days (263, 535, 746). Hamsters are more resistant 1
and require larger doses to induce t mice, occurring between 16 and 24 hours and lasting 7
about 5 days (263, 535, 746). Hamsters are more resistant 1
and require larger doses to induce the response whereas d
dogs are completely resistant to the cholestatic e about 5 days (263, 535, 746). Hamsters are more resistant 104
and require larger doses to induce the response whereas dis-
dogs are completely resistant to the cholestatic effects of
acute ANIT administration (535). Even b and require larger doses to induce the response whereas didgs are completely resistant to the cholestatic effects of acute ANIT administration (535). Even before cessation dof bile flow, ANIT produces retention of BSP (84) 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 acute ANIT administration (535). Even before cessation of bile flow, ANIT produces retention of BSP (84) an bilirubin (991) in plasma by affecting hepatic uptake the exogenously administered compound. In addition ANIT incr of bile flow, ANIT produces retention of BSP (84) and b
bilirubin (991) in plasma by affecting hepatic uptake of C
the exogenously administered compound. In addition, n
ANIT increases plasma alanine aminotransferase activbilirubin (991) in plasma by affecting hepatic uptake of (
the exogenously administered compound. In addition,
ANIT increases plasma alanine aminotransferase activ-
ity in rats (263) and dogs (535). Concentrations of 5'-
n the exogenously administered compound. In addition, respectively in rats (263) and dogs (535). Concentrations of 5'-
ity in rats (263) and dogs (535). Concentrations of 5'-
nucleotidase (263), BSP, and taurocholate (684) i ANIT increases plasma alanine aminotransferase activity in rats (263) and dogs (535) . Concentrations of $5'$ - the nucleotidase (263) , BSP, and taurocholate (684) increase actin plasma after ANIT administration thu ity in rats (263) and dogs (535). Concentrations of 5'-
nucleotidase (263), BSP, and taurocholate (684) increase act
in plasma after ANIT administration thus indicating (
that increased leakage across the tight junctions nucleotidase (263), BSP, and taurocholate (684) increase as
in plasma after ANIT administration thus indicating
that increased leakage across the tight junctions may lo
contribute to the regurgitation of these substances in plasma after ANIT administration thus indicating C
that increased leakage across the tight junctions may loid
contribute to the regurgitation of these substances and secr
enzymes in blood (684). Incorporation of radiol 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 A contribute to the regurgitation of these substances and second endiversions in blood (684). Incorporation of radiolabeled δ -
aminolevulinic acid into bilirubin increases after ANIT revadministration in a dose-related m 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 aminolevulinic acid into bilirubin increases after ANIT
administration in a dose-related manner (993). This sug-
gests that enhanced bilirubin synthesis may also be
involved in drug-induced hyperbilirubinemia. Finally,
ANI 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, involved in drug-induced hyperbilirubinemia. Finally
ANIT causes an impairment of microsomal enzyme ac
tivity (150, 263, 432, 929).
Pretreatment of rats with inhibitors of protein and
RNA synthesis block ANIT-induced hyper

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 tivity (150, 263, 432, 929).

Pretreatment of rats with inhibitors of protein

RNA synthesis block ANIT-induced hyperbilirubin

and cholestasis (536, 1186). A direct effect of thes

hibitors on the enzymes involved in ANIT Pretreatment of rats with inhibitors of protein and
RNA synthesis block ANIT-induced hyperbilirubinemia
and cholestasis (536, 1186). A direct effect of these in-
hibitors on the enzymes involved in ANIT biotransfor-
mation RNA synthesis block ANIT-induced hyperbilirubinemia ph
and cholestasis (536, 1186). A direct effect of these in-
hibitors on the enzymes involved in ANIT biotransfor-
toor mation is possible (156, 748, 1095) but not comple and cholestasis (536, 1186). A direct effect of these in-
hibitors on the enzymes involved in ANIT biotransfor-
mation is possible (156, 748, 1095) but not completely
established. However, these inhibitors do not affect ea (537). established. However, these inhibitors do not affect early
BSP retention or prolong pentobarbital-sleeping time
(537).
Hepatic clearance of exogenously administered biliru-

bin is reduced in ANIT-treated rats and mice before

THE MANU BILIARY EXCRETION 15
the maximal rate of bilirubin excretion into bile is sig-
nificantly diminished. ANIT decreases the uptake of NE AND BILIARY EXCRETION 15
the maximal rate of bilirubin excretion into bile is sig-
nificantly diminished. ANIT decreases the uptake of
bilirubin into the liver even in mice with bile duct ligation 15
the maximal rate of bilirubin excretion into bile is sig-
nificantly diminished. ANIT decreases the uptake of
bilirubin into the liver even in mice with bile duct ligation
but does not influence bilirubin conjugation. T 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, 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, nificantly 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, 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 mechani but does not influence bilirubin conjugatio
appears to have a direct effect on hepatic u
and biliary excretion. However, the mec
acute action of ANIT is complex and furt
needed to clarify the causes of cholestasis
b. CHOLE pears to have a direct effect on hepatic uptake, storaged biliary excretion. However, the mechanism of the use of cholest
action of ANIT is complex and further studies a
eded to clarify the causes of cholestasis.
b. CHOLEP

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 chole-
philic organic an acute action of ANIT is complex and further studies are
needed to clarify the causes of cholestasis.
b. CHOLEPHILIC ANIONS. Hepatic transport of chole-
philic organic anions has been widely studied to elucidate
the mechani needed to clarify the causes of cholestasis.
b. CHOLEPHILIC ANIONS. Hepatic transport of chephilic organic anions has been widely studied to elucid
the mechanisms of bile production, hepatic uptake,
elimination. Indocyanin b. CHOLEPHILIC ANIONS. Hepatic transport of chole-
philic organic anions has been widely studied to elucidate
the mechanisms of bile production, hepatic uptake, and
elimination. Indocyanine green, rose bengal, unconju-
gat philic organic anions has been widely studied to elucidate
the mechanisms of bile production, hepatic uptake, and
elimination. Indocyanine green, rose bengal, unconju-
gated BSP, and bromcresol green are cholestatic in ra the mechanisms of bile production, hepatic uptake, and
elimination. Indocyanine green, rose bengal, unconju-
gated BSP, and bromcresol green are cholestatic in rats
and mice, and eosine decreases bile flow only in mice
wh 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 c gated 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 mic 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). Choleph 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 cholestati 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 choleret 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 accumu have a low biliary T_m tend to be cholestatic while tho with a high biliary T_m tend to be choleretic (428). The cholestatic effect appears to be due to accumulation cholephils in the liver because of their limited rate 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 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 inhibiti 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 $(25, 149, 425, 428, 60$ 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, 7 fested 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 cholesta

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 1044). Other possible mechanisms for cholestasis are discussed in the review of Plaa and Priestly (928).

c. MISCELLANEOUS. Experimental hypothermia in-

duced by administration of anesthetics to rats decreases

bile flow discussed in the review of Plaa and Priestly (928).

c. MISCELLANEOUS. Experimental hypothermia

duced by administration of anesthetics to rats decree

bile flow and biliary excretion of bilirubin and BSP (9

Other studies c. MISCELLANEOUS. Experimental hypothermia in-
duced 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 hypother-
 duced 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 hypother-
mia markedly reduces bile flow, bile acid excre 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.

NIT causes an impairment of microsomal enzyme ac-

into intercellular space during phalloidin-induced cho-

lestasis. Rats made cholestatic by bile duct ligation sur-

Pretreatment of rats with inhibitors of protein and vi Cholestasis can be induced by administration of phalbile 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 phal-
loidin to rats (268, 269, 297, 312). A decrease in thought to be due to a decrease in $Na⁺-K⁺-ATPase$
activity.
Cholestasis can be induced by administration of phal-
loidin to rats (268, 269, 297, 312). A decrease in bile acid
secretion and an increase in the bile/pla activity.
Cholestasis can be induced by administration of phal-
loidin 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 fr Cholestasis can be induced by administration of phaloidin to rats (268, 269, 297, 312). A decrease in bile acise
cretion and an increase in the bile/plasma ratios complex that sepa-
inulin and sucrose are observed. Freeze 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 sepasecretion and an increase in the bile/plasma ratios of
inulin and sucrose are observed. Freeze fracture replicas
reveal alterations of the junctional complex that sepa-
rates the canalicular lumen from the lateral intercel inulin and sucrose are observed. Freeze fracture replicas
reveal alterations of the junctional complex that sepa-
rates the canalicular lumen from the lateral intercellular
space. A microfilament-mediated change in junctio reveal alterations of the junctional complex that sep-
rates the canalicular lumen from the lateral intercellula
space. A microfilament-mediated change in junction
permeability might permit efflux of biliary constituen
int space. A microfilament-mediated change in junctional permeability might permit efflux of biliary constituents
into intercellular space during phalloidin-induced cho-
lestasis. Rats made cholestatic by bile duct ligation sur-
vive phalloidin poisoning because uptake of demeth vive phalloidin poisoning because uptake of demethylinto intercellular space during phalloidin-induced chestasis. Rats made cholestatic by bile duct ligation survive phalloidin poisoning because uptake of demethy phalloin is depressed 75% after 4 hours of ligation (1228 Bil lestasis. Rats made cholestatic by bile duct ligation sur
vive phalloidin poisoning because uptake of demethyl
phalloin is depressed 75% after 4 hours of ligation (1228)
Bile acids prevent phalloidin toxicity in isolated

BSP retention or prolong pentobarbital-sleeping time into bile in 4 hours. Bile flow decreases after 90 minutes (537).

and is completely stopped by 4 hours, indicating complete

Hepatic clearance of exogenously administer tocytes (366) by inhibition of toxin uptake (916, 918).
Aflatoxin B₁ is rapidly taken up by isolated perfused phalloin is depressed 75% after 4 hours of ligation (1228).
Bile acids prevent phalloidin toxicity in isolated hepa-
tocytes (366) by inhibition of toxin uptake (916, 918).
Aflatoxin B_1 is rapidly taken up by isolated 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 excre tocytes (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 Aflatoxin B_1 is repriat livers and approximate in 4 hours.

and is completely stochalostasis (1193).

The antibiotics,

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

KLAASSEN AND WATKINS
be due to inhibition of hepatic uptake of organic anions bile acid synthesis or degradation, intestina
or inhibition of UDP-glucuronosyltransferase (41, 703, pathways, and the enterohepatic circulation KLAASSEN AN
be due to inhibition of hepatic uptake of organic anions
or inhibition of UDP-glucuronosyltransferase (41, 703,
1104). Rifampicin reduced the biliary excretion of war-KLAASSEN
be due to inhibition of hepatic uptake of organic anions
or inhibition of UDP-glucuronosyltransferase (41, 703
1104). Rifampicin reduced the biliary excretion of war-
farin by 56% (1284). be due to inhibition of
or inhibition of UDP
1104). Rifampicin red
farin by 56% (1284).
The oral hypoglyce due to inhibition of hepatic uptake of organic ani
inhibition of UDP-glucuronosyltransferase (41, 7
04). Rifampicin reduced the biliary excretion of w
rin by 56% (1284).
The oral hypoglycemic drugs, carbutamide, chlorpro-

or inhibition of UDP-glucuronosyltransferase (41, 703, 1104). Rifampicin reduced the biliary excretion of war-
farin by 56% (1284).
The oral hypoglycemic drugs, carbutamide, chlorpro-
pamide, and tolbutamide, produce a ver 1104). Rifampicin reduced the biliary excretion of v
farin by 56% (1284).
The oral hypoglycemic drugs, carbutamide, chlorp
pamide, and tolbutamide, produce a very low incide
of hepatic reactions including elevated alkaline farin by 56% (1284).
The oral hypoglycemic drugs, carbutamide, chlorpropamide, and tolbutamide, produce a very low incidence
of hepatic reactions including elevated alkaline phospha-
tase activity and cholestatic jaundice The oral hypoglycemic drugs, carbutamide, chlorpro-
pamide, and tolbutamide, produce a very low incidence
of hepatic reactions including elevated alkaline phospha-
tase activity and cholestatic jaundice (709). Endotoxin
in pamide, and tolbutamide, produce a very low incidence of hepatic reactions including elevated alkaline phosphatase activity and cholestatic jaundice (709). Endotoxin is from *Escherichia coli* decreases bile flow in the i of hepatic reactions including elevated alkaline phospha-
tase activity and cholestatic jaundice (709) . Endotoxin
from *Escherichia coli* decreases bile flow in the isolated
merfused liver of the rat (1195) which may tase activity and cholestatic jaundice (709). Endotor
from *Escherichia coli* decreases bile flow in the isolat
perfused liver of the rat (1195) which may be account
for by a decrease in Na⁺-K⁺-ATPase (1196). Since t
e 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 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 indocy-
anine green clearance, circulating endotoxin may con-
tri for by a decrease in Na^+ -K⁺-ATPase (1196). Since the bilendotoxin also causes impairment of BSP and indocy-
anine green clearance, circulating endotoxin may con-
tribute to the production of intrahepatic cholestasis o endotoxin also causes impairment of BSP and indo
anine green clearance, circulating endotoxin may c
tribute to the production of intrahepatic cholestasis
served during bacterial infection (1197). Endotoxin
concentrated in anine green clearance, circulating endotoxin may contribute to the production of intrahepatic cholestasis of served during bacterial infection (1197). Endotoxin concentrated in liver because two thirds of an intranous dose tribute 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 adminis served during bacterial infection (1197) . Endotoxin is concentrated in liver because two thirds of an intrave-
nous dose is recovered in the organ 8 hours after administration while about 7% is excreted into bile $(7$ concentrated i
nous dose is re
istration while
However, the
main obscure.
In allergic us dose is recovered in the organ 8 hours after administration while about 7% is excreted into bile (76 owever, the mechanisms for uptake and secretion in obscure.
In allergic hepatitis, lymphocytes elaborate macro--------

However, the mechanisms for uptake and secretion remain obscure.
In allergic hepatitis, lymphocytes elaborate macro-
phage migration inhibitory factor which, when adminis-
tered via a mesenteric vein in rats, produces a ma tered via a mesenteric vein in rats, produces a marked
reduction in bile flow and bile acid secretion (815). His-
pholipids (162, 843, 1097, 1098, 1100). Solubility of cho-
tological changes resemble those for intrabanatic main obscure.
In allergic hepatitis, lymphocytes elaborate macro-
phage migration inhibitory factor which, when adminis-
tered via a mesenteric vein in rats, produces a marked
reduction in bile flow and bile acid secretion In allergic hepatitis, lymphocytes elaborate macr
phage migration inhibitory factor which, when adminitered via a mesenteric vein in rats, produces a mark
reduction in bile flow and bile acid secretion (815). Hi
tological phage migration inhibitory factor which, when administered via a mesenteric vein in rats, produces a marked reduction in bile flow and bile acid secretion (815). His-
tological changes resemble those for intrahepatic chol tered via a mesenteric vein in rats, produces a marked
reduction in bile flow and bile acid secretion (815). His-
tological changes resemble those for intrahepatic chole-
stasis and include dilatation of bile canaliculi an 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 lympho tological changes resemble those for intrahepatic chole-
stasis and include dilatation of bile canaliculi and loss of
microvilli. This factor is not produced by lymphocytes
from normal patients. The mechanism whereby this ration and include dila
microvilli. This facto.
from normal patients.
tor from patients wit
rats is not understood
Recently, the tetrad icrovilli. This factor is not produced by lymphocytom normal patients. The mechanism whereby this far from patients with hepatitis induces cholestasis is is not understood.
Recently, the tetradecapeptide hormone, somatosta from normal patients. The mechanism whereby this factor from patients with hepatitis induces cholestasis in of rats is not understood. Summer in the tetradecapeptide hormone, somatostatin, the was shown to inhibit basal a

tor 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). Studi rats is not understood.

Recently, the tetradecapeptide hormone, somatostatin, the was shown to inhibit basal and food-stimulated biliary

secretion in the dog (806). Studies in rats indicate somatostatin decreases bile f Recently, the tetradecapeptide hormone, somatostatin, the was shown to inhibit basal and food-stimulated biliary lescretion in the dog (806). Studies in rats indicate somatostatin decreases bile flow by 30%, bile acid sec was shown to inhibit basal and food-stimulated biliary
secretion in the dog (806). Studies in rats indicate so-
matostatin decreases bile flow by 30%, bile acid secretion
by 35% to 45%, and the bile acid-independent fract secretion in the dog (806). Studies in rats indicate somatostatin decreases bile flow by 30%, bile acid secretio
by 35% to 45%, and the bile acid-independent fraction
of canalicular bile flow. Endogenous bilirubin excretio matostatin 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-induce by 35% to 45%, and the bile acid-independent fraction of canalicular bile flow. Endogenous bilirubin excretion 6 is not affected (984). A similar somatostatin-induced edecrease in bile flow has been observed in dogs (502) of canalicular bile flow. Endogenous bilirubin excretic
is not affected (984). A similar somatostatin-induce
decrease in bile flow has been observed in dogs (502
Other natural products that induce cholestasis includ
icter is not affected
decrease in bild
Other natural
icterogenin, 22
desmin (283).
Effects of et crease in bile flow has been observed in dogs (502) .

her natural products that induce cholestasis include

erogenin, 22 β -angeloyloxyoleanolic acid, and spori-

smin (283).

Effects of ethanol on bile formation have Other natural products that induce cholestasis include
icterogenin, 22 β -angeloyloxyoleanolic acid, and spori-
desmin (283).
Effects of ethanol on bile formation have been re-
viewed recently (1147). Acute administrati

icterogenin, 22 β -angeloyloxyoleanolic acid, and spori-
desmin (283). of
Effects of ethanol on bile formation have been re-
viewed recently (1147). Acute administration produces bile
an apparent dose-related reduction desmin (283). of
Effects of ethanol on bile formation have been re-
viewed recently (1147). Acute administration produces bi
an apparent dose-related reduction in bile flow and bile
acid secretion in dogs, rats, and humans Effects of ethanol on bile formation have been re-
viewed recently (1147). Acute administration produces bile
an apparent dose-related reduction in bile flow and bile 107
acid secretion in dogs, rats, and humans. The acute viewed recently (1147). Acute administration produces b
an apparent dose-related reduction in bile flow and bile 1
acid secretion in dogs, rats, and humans. The acute m
response is present even if the animal has been fed t an apparent dose-related reduction in bile flow and bile 10 acid secretion in dogs, rats, and humans. The acute m
response is present even if the animal has been fed te
alcohol chronically. This cholestastic effect is p acid secretion in dogs, rats, and humans. The acute met
response is present even if the animal has been fed
alcohol chronically. This cholestastic effect is probably com
due to inhibition of bile acid-dependent secretion. response is present even if the animal has been
alcohol chronically. This cholestastic effect is proba
due to inhibition of bile acid-dependent secretion. Bili
excretion of BSP and indocyanine green is decreased
acute etha 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
pacute ethanol administration. Elimination of pro due to inhibition of bile acid-dependent secretion. Biliary of bilirexcretion of BSP and indocyanine green is decreased by propon
acute ethanol administration. Elimination of propoxy- may a
phene (864) and lorazepam (510) excretion of BSP and indocyanine green is decreased lacute ethanol administration. Elimination of propox phene (864) and lorazepam (510) on first pass through
the liver is decreased during acute ethanol infusions. Loethano acute ethanol administration. Elimination of propoxy-
phene (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 meth phene (864) and lorazepam (510) on first pass through humans (281). In addition, the functional integrity of the
the liver is decreased during acute ethanol infusions. Low gallbladder is important in maintaining normal bi the liver is decreased during acute ethanol infusions. Low nisms for this effect involve alterations in rates of hepatic

bile acid synthesis or degradation, intestinal metabolic p warkins
bile acid synthesis or degradation, intestin
pathways, and the enterohepatic circulation
Although the central theme of this revie

WATKINS
le acid synthesis or degradation, intestinal metabolic
thways, and the enterohepatic circulation.
Although the central theme of this review is biliary
cretion, understanding the proposed mechanisms of explore 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 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 ass 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 excr 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 dis-
cussi excretion, understanding the proposed mechanisms of
cholestasis assists our comprehension of bile formation
and biliary excretion. Based on the aforementioned dis-
cussion, the following mechanisms may be involved in-
intr cholestasis assists our comprehension of bile formation
and biliary excretion. Based on the aforementioned dis-
cussion, the following mechanisms may be involved in-
intrahepatic cholestasis: 1) impairment of sinusoidal
me 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 in cussion, the following mechanisms may be involved in
intrahepatic cholestasis: 1) impairment of sinusoida
membrane function of hepatic uptake; 2) interference
with intracellular binding and distribution; 3) altere
bile aci 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
m 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
m with intracellular binding and distribution; 3) altere
bile acid metabolism; 4) interference with mitochondria
energy supply; 5) morphological changes in canalicula
membrane such as loss of microvilli and membrane er
zymes bile acid metabolism; 4) interference with mitochondriant energy supply; 5) morphological changes in canalicula
membrane such as loss of microvilli and membrane energy
mes; 6) disruption of microtubule and microfilamer
for energy supply; 5) morphological changes in ca
membrane such as loss of microvilli and membranes; 6) disruption of microtubule and micro
formation and function; and 7) interference w
licular bile elaboration (928, 972, 1028 *Crymes*; 6) disrupt
Cymes; 6) disrupt
formation and fu
C. Cholelithiasis
Cholelithiasis,

formation and function; and 7) interference with cana-
licular bile elaboration (928, 972, 1028, 1054).
C. Cholelithiasis, or gallstone disease, is associated with
cholelithiasis, or gallstone disease, is associated with
 instead of the elaboration (928, 972, 1028, 1054).

1 C. Cholelithiasis

Cholelithiasis, or gallstone disease, is associated within

cholelithiasis, or gallstone disease, is associated within

solid constituent of gallston 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 b C. 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 Cholelithiasis, or gallstone disease, is associated with insolubility of cholesterol since it is the predominar solid constituent of gallstones (88, 1153). Cholesterol maintained in solution in bile by formation of mixe mi 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 ph 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 maintained in solution in bile by formation of mixemicelles consisting of bile acids, cholesterol, and phospholipids (162, 843, 1097, 1098, 1100). Solubility of cholesterol depends on the relative concentrations of thes th micelles consisting of bile acids, cholesterol, and phe
pholipids (162, 843, 1097, 1098, 1100). Solubility of ch
lesterol depends on the relative concentrations of the
three biliary constituents. This relationship can be i pholipids (162, 843, 1097, 1098, 1100). Solubility of cho-
lesterol depends on the relative concentrations of these
three biliary constituents. This relationship can be illus-
trated by triangular coordinates (fig. 5) whic lesterol depends on the relative concentrations of these
three biliary constituents. This relationship can be illus-
trated by triangular coordinates (fig. 5) which can distin-
guish bile from patients with cholesterol sto three biliary constituents. This relationship can be illus-
trated by triangular coordinates (fig. 5) which can distin-
guish bile from patients with cholesterol stones from bile
of those without (17). Bile from patients w trated 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, 120 guish bile from patients with cholesterol stoined of those without (17). Bile from patients we supersaturated with cholesterol (1102, 120') the predominant components of biliary calcitum salts (1153). Lithogenesis results supersaturated with cholesterol (1102, 1207, 1208) and
the predominant components of biliary calculi are cho-
lesterol and insoluble calcium salts (1153).
Lithogenesis results from some metabolic defect in
liver and may be supersaturated with cholesterol (1102, 1207, 1208) and
the predominant components of biliary calculi are cho-
lesterol and insoluble calcium salts (1153).
Lithogenesis results from some metabolic defect in
liver and may be

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the predominant components of biliary calculi are cho-
lesterol and insoluble calcium salts (1153).
Lithogenesis results from some metabolic defect in
liver and may be due to excessive synthesis and excretion
of cholestero lesterol 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, 85 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 synthes 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 e $602, 853, 961, 1089, 1207, 1208$. 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 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 ac excretion of cholesterol are the predominant events in obese patients (107). However, in the majority of gall-
stone-forming patients, diminished secretion of bile acids
is a fundamental defect that reduces the total body obese patients (107). However, in the majority of gall-
stone-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 ac stone-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 frequ is a fundamental defect that reduces the total body
of bile acids (1207, 1208). Currently, the most acce
view is that there is an increased cycling frequenc
bile acids which suppresses bile acid synthesis (816,
1071). Enz of bile acids (1207, 1208). Currently, the most accept
view is that there is an increased cycling frequency
bile acids which suppresses bile acid synthesis (816, 8
1071). Enzymatic activities of hepatic β -hydroxy
methy 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 chol bile acids which suppresses bile acid synthesis (816, 856, 1071). Enzymatic activities of hepatic β -hydroxy- β -methylglutaryl-CoA reductase are higher, and choles-terol-7- α -hydroxylase lower, in patients with gall 1071). Enzymatic activities of hepatic β -hydroxy- β -methylglutaryl-CoA reductase are higher, and choles-
terol-7- α -hydroxylase lower, in patients with gallstones
compared to those without (849). Defective conjugat methylglutaryl-CoA reductase are higher, and choles-
terol-7- α -hydroxylase lower, in patients with gallstones
compared to those without (849). Defective conjugation
of bilirubin monoglucuronide could result in an incre terol-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 b 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 formatio of bilirubin monoglucuronide could result in an increase
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 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 bi 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 com-
position (930). Micellar binding accounts for 80% humans (281). In addition, the functional integrity of the gallbladder is important in maintaining normal bile com-
position (930). Micellar binding accounts for 80% of the
calcium in hepatic bile but only 50% in gallbladd gallbladder is important in maintaining normal bile com-
position (930). Micellar binding accounts for 80% of the
calcium in hepatic bile but only 50% in gallbladder bile,
suggesting that calcium binding in soluble micelle position (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

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acids, cholesterol, and phospholipids. Bile from patients with choles-100 **4 PERCENT BILE SALTS**
FIG. 5. Triangular coordinates illustrating the relations
acids, cholesterol, and phospholipids. Bile from patients w
terol stones can be distinguished from bile of those without. FINCENT BILE SALTS WELL TO THE TRANSPART TO THE SALTS THE SALTS TO THE SALTS THE SALTS OF THE SALTS CONTRACT THE SALTS CONTRACT AND SACT AND SALTS WELL SALTS WERE SALTS WELL SALTS (1218) and estrogens (88) increases the li

FIG. 5. Triangular coordinates illustrating the relationship of bile
acids, cholesterol, and phospholipids. Bile from patients with choles-
terol stones can be distinguished from bile of those without.
clofibrate (218) and dends, cholesterol, and phospheterol stones can be distinguished
clofibrate (218) and estrephicity of bile and has
incidence of cholelithiasi
Medical treatment of Medical treatment of gallstones has been associated with a high eidence of cholelithiasis.
Medical treatment of gallstones has been reviewed, d drug therapy is directed toward decreasing the lith-

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 towar genicity 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 lith-

ogenicity of bile by increasi incidence of cholelithiasis. the Medical treatment of gallstones has been reviewed, of and drug therapy is directed toward decreasing the lith-
ogenicity of bile by increasing the bile acid pool (123, de
499, 1098). Chroni Medical treatment of gallstones has been reviewed,
and drug therapy is directed toward decreasing the lith-
ogenicity of bile by increasing the bile acid pool (123,
499, 1098). Chronic administration of exogenous bile
acid and drug therapy is directed toward decreasing the lith-
ogenicity of bile by increasing the bile acid pool (123,
499, 1098). Chronic administration of exogenous bile
acids to man (taurocholate, 380; chenodeoxycholate, 64, ogenicity 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, 325 499, 1098). Chronic administration of exogenous bile chencids to man (taurocholate, 380; chenodeoxycholate, 64, resu
220, 229, 540, 550, 775, 1173; ursodeoxycholate, 47, 325, circle
326, 544, 768, 770, 780, 1020, 1138) de acids to man (taurocholate, 380; chenodeoxycholate, 64
220, 229, 540, 550, 775, 1173; ursodeoxycholate, 47, 325
326, 544, 768, 770, 780, 1020, 1138) decreases cholesterc
saturation in bile and induces gallstone dissolution 220, 229, 540, 550, 775, 1173; ursodeoxycholate, 47, 3:
326, 544, 768, 770, 780, 1020, 1138) decreases choleste
saturation in bile and induces gallstone dissolution
the majority of patients with radiolucent gallstones. Lit 326, 544, 768, 770, 780, 1020, 1138) decreases cholesterol
saturation in bile and induces gallstone dissolution in
the majority of patients with radiolucent gallstones. Lith-
ogenicity is reduced decreasing the proportion saturation in bile and induces gallstone dissolution in
the majority of patients with radiolucent gallstones. Lith-
ogenicity is reduced decreasing the proportion of choles-
terol relative to bile acids and lecithin (13) a the majority of patients with radiolucent gallstones. Lith-
ogenicity is reduced decreasing the proportion of choles-
terol relative to bile acids and lecithin (13) and perhaps
by reducing hydroxymethylglutaryl-CoA reducta ogenicity is reduced decreasing the proportion of cholend terol relative to bile acids and lecithin (13) and perhaby reducing hydroxymethylglutaryl-CoA reductase (6 1020). Correlation between cholesterol and bile acid cret cretion suggests cholesterol transfer across the canalic-
ular membrane is best explained on the basis of incor-
poration into lecithin-bile acid mixed micelles (461).
Secretion of these lipids depends on bile acid secreti 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 incorpora 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). to cretion suggests cholesterol transfer across the canalic-
ular membrane is best explained on the basis of incor-
poration into lecithin-bile acid mixed micelles (461). te:
Secretion of these lipids depends on bile acid sec ular membrane is best explained on the basis of incor-
poration into lecithin-bile acid mixed micelles (461).
Secretion of these lipids depends on bile acid secretion
(262, 1246, 1250). However, bile acid secretion rate
(1 poration into lecithin-bile acid mixed micelles (461). temic circulation. In addition to extraction and/or bio-
Secretion of these lipids depends on bile acid secretion transformation in the liver, metabolism in intestine composition. **Theory.** Theory. Theorem, blue acts ecclesion,

bile acid structure (390, 496, 1103), and spinal being studied (91, 1173) can all alter bile
 VI. Hepatic Elimination of Xenobiotics

liver probably developed evolutionari animal being studied (91, 1173) can all alter bile lipid
mposition.
VI. Hepatic Elimination of Xenobiotics
The liver probably developed evolutionarily as a union ex
a secretory diverticulum of gut endoderm and as a to

to oth

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

Murdraining VI. Hepatic Elimination of AenoDiotics
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 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 (of a secretory diverticulum of gut endoderm and as a to
storage organ, and the hepatic portal venous system
draining the intestines preceded formation of a proper a
liver (33). The anatomical position of this organ is parstorage organ, and the hepatic portal venous system
draining the intestines preceded formation of a proper
liver (33). The anatomical position of this organ is par-
positionally advantageous for removing toxicants from the draining the intestines preceded formation of a proper
liver (33). The anatomical position of this organ is par-
licularly advantageous for removing toxicants from the
blood after absorption by the gastrointestinal tract. liver (33). The anatomical position of this organ is particularly advantageous for removing toxicants from the 7
blood after absorption by the gastrointestinal tract. Since p
blood from the intestine passes through the liv ticularly advantageous for removing toxicants from the 76
blood after absorption by the gastrointestinal tract. Since
blood from the intestine passes through the liver prior (1
to systemic circulation, the liver can theore

o excretion. Experiments in which the chemical was ad-BILE FORMATION, HEPATIC UPTAKE, AND BILIARY EXCRETION 17
17
 $\mathcal{P}(\bigwedge \setminus$ prevent distribution to other parts of the body. The liver
is also unique in that chemicals in plasma come in direct is also unique in that chemicals in plasma come in the chemicals in plasma come in direct
is also unique in that chemicals in plasma come in direct
contact with the hepatocytes which are not separated ity and the Hallary EXCRETION 17
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 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 organ 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 organ 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 ex-
c contact with the hepatocytes which are not separate
from the plasma by vascular tissue as in other organ
Chemicals entering the systemic circulation may be e:
creted by the kidney or liver or may be biotransforme
prior to from the plasma by vascular tissue as in other organs.
Chemicals entering the systemic circulation may be ex-
creted by the kidney or liver or may be biotransformed
prior to excretion. Factors determining whether a xeno-
b Chemicals entering the systemic circulation may be excreted by the kidney or liver or may be biotransformed
prior to excretion. Factors determining whether a xeno-
biotic is eliminated via urine or bile are largely unknown creted by the kidney or liver or may be biotransformed
prior to excretion. Factors determining whether a xeno-
biotic is eliminated via urine or bile are largely unknown
(245, 246, 1114). The relative importance of either prior to excretion. Factors determining whether a xeno-
biotic 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 difficul biotic 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 aft (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 in the excretion of foreign compounds is difficult ascertain. Studies have often drawn conclusions aft quantifying the amount of chemical in urine or feces.
experiments where a chemical was administered oral and later foun 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 excrequantifying 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 excre-
tion was often minimized by concluding that the fecal experiments where a chemical was administered orally
and later found in feces, the importance of biliary excre-
tion was often minimized by concluding that the fecal
fraction resulted from poor absorption and not biliary
e and later found in feces, the importance of biliary excretion was often minimized by concluding that the fectration resulted from poor absorption and not biliar excretion. Experiments in which the chemical was as ministere tion was often minimized by concluding that the fecal
fraction resulted from poor absorption and not biliary
fractoin estimation and inclusion and the distinguished
ministered intravenously are generally easier to inter-
 fraction resulted from poor absorption and not biliatex-
excretion. Experiments in which the chemical was a
ministered intravenously are generally easier to int
pret. However, the importance of biliary excretion m
not be r 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 entero-hepatic ministered intravenously are generally easier to inter-
pret. However, the importance of biliary excretion may
not be recognized if the compound undergoes an entero-
hepatic circulation and is eventually cleared from the
b not be recognized if the compound undergoes an entero-
hepatic 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 not be recognized if the compound undergoes an entero-
hepatic 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 hepatic 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 body by the kidneys and may be overestimated if th
chemical is excreted across the intestinal wall rathe
than into bile (1008, 1009). Thus, accurate determination
of the role that biliary excretion plays in the elimination 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 experim 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 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 the 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
ci design which permits analysis of bile for cont
chemical and its metabolites and evaluation
results in relation to experiments where ente
circulation, plasma disappearance, and urinary
excretion of that compound are also me *A. First-Pass Effect*
A. First-Pass Effect
The liver is capable

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 Mumerous chemicals are 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 phenomen in origination 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 pr A. First-Pass Effect
The liver is capable of removing chemicals from bloo
in one pass through the liver. This phenomenon has bee
called the "first-pass effect" or presystemic hepatic elim-
ination (385, 386). All chemicals 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 elim-
ination (385, 386). All chemica 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 elim-
ination (385, 386). All chemicals absorbed from the in one pass through the liver. This phenomenon has been
called the "first-pass effect" or presystemic hepatic elim-
ination (385, 386). All chemicals absorbed from the gas-
trointestinal tract, except for the mouth and rec called the "first-pass effect" or presystemic hepatic elimination (385, 386). All chemicals absorbed from the gas-
trointestinal tract, except for the mouth and rectum,
pass through the liver before reaching the general sy ination (385, 386). All chemicals absorbed from the gas-
trointestinal tract, except for the mouth and rectum,
pass through the liver before reaching the general sys-
temic circulation. In addition to extraction and/or bio trointestinal tract, except for the mouth and rectum,
pass through the liver before reaching the general sys-
temic circulation. In addition to extraction and/or bio-
transformation in the liver, metabolism in intestine an pass through the liver before reaching the general systemic circulation. In addition to extraction and/or bio-
transformation in the liver, metabolism in intestine and
lung and excretion by the lung can also contribute to
 temic circulation. In addition to extraction and/or bio-
transformation in the liver, metabolism in intestine and
lung and excretion by the lung can also contribute to
presystemic elimination. Theoretically, the liver can transformation in the liver, metabolism in intestine and
lung and excretion by the lung can also contribute to
presystemic elimination. Theoretically, the liver can re-
move xenobiotics from the blood after absorption from lung and excretion by the lung can also contribute the presystemic elimination. Theoretically, the liver can refluence interior and prevent their distribution from the gastrointestinal tract and prevent their distribution presystemic elimination. Theoretically, the liver can re-
move xenobiotics from the blood after absorption from
the gastrointestinal tract and prevent their distribution
to other parts of the body. However, large interindi move 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 the gastrointestinal tract and prevent their distributive to other parts of the body. However, large interindividual
differences in first-pass effect due to variations in hepa
extraction ratios permit different amounts of other parts of the body. However, large interindividual
fferences in first-pass effect due to variations in hepatic
traction ratios permit different amounts of a chemical
enter the systemic circulation in different patient differences in first-pass effect due to variations in hepatiex
traction ratios permit different amounts of a chemica
to enter the systemic circulation in different patients.
Numerous chemicals are known or expected to unde

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 com-
po to enter the systemic circulation in different patients.

Numerous chemicals are known or expected to undergo

a first-pass effect. These include physiological com-

pounds such as bile acids (21, 36, 393, 497, 498, 528, 5 Numerous chemicals are known or expected to undergo
a first-pass effect. These include physiological com-
pounds such as bile acids (21, 36, 393, 497, 498, 528, 542,
769, 779, 879, 943), and the pharmacological agents proa first-pass effect. These include physiological com-
pounds such as bile acids (21, 36, 393, 497, 498, 528, 542,
769, 779, 879, 943), and the pharmacological agents pro-
pranolol (1075, 1076), lidocaine (1134), oxyphenbut pounds 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) 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), imipr Downloaded from pharmrev.aspetjournals.org at Thammasart University on December 8, 2012

(841), methyltestosterone (31), alprenolol (437), mor-KLAASSEN AND

(841), methyltestosterone (31), alprenolol (437), mor-

phine (542), nalorphine (543), pentazocine (293), ouabain in

(526), phenol-3,6-dibromphthalein disulfonate (526), m KLAASSEN AI
(841), methyltestosterone (31), alprenolol (437), mor-
phine (542), nalorphine (543), pentazocine (293), ouabain
(526), phenol-3,6-dibromphthalein disulfonate (526),
amaranth (526), insulin (1187), diethylstilb amaranth (541), methyltestosterone (31), alprenolol (437), morphine (542), nalorphine (543), pentazocine (293), ouabain (526), phenol-3,6-dibromphthalein disulfonate (526), amaranth (526), insulin (1187), diethylstilbestro (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) phine (542), nalorphine (543), pentazocine (293), ouabain indicate (526), phenol-3,6-dibromphthalein disulfonate (526), many chamaranth (526), insulin (1187), diethylstilbestrol (1176), and systethinylestradiol (484), Org (526), phenol-3,6-dibromphthalein disulfonate (526), maand amaranth (526), insulin (1187), diethylstilbestrol (1176), and ethinylestradiol (484), Org 6368 (20), prazosin (1011), C and manganese chloride (1175). In fact, m amaranth (526), insulin (1187), diethylstilbestrol (117
ethinylestradiol (484), Org 6368 (20), prazosin (101
and manganese chloride (1175). In fact, more than 9
of a low dose of propranolol is cleared from blood afte
singl ethinylestradiol (484), Org 6368 (20), prazosin (1011), C
and manganese chloride (1175). In fact, more than 90% com
of a low dose of propranolol is cleared from blood after a zen
single pass through the liver (1073). Howev and manganese chloride (1175). In fact, more than 90% completely removed per unit time (1263). At steady state, of a low dose of propranolol is cleared from blood after a venobiotic elimination by the liver can be estimat of a low dose of propranolol is cleared from blood after a
single pass through the liver (1073). However, presys-
temic elimination of propranolol appears saturable; no
drug is found in the systemic blood when a dose of 0. single pass through the liver (1073). However, presys-
temic 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.
Wit temic 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
propr drug is found in the systemic blood when a dose of 0.
mg/kg is administered to humans or 40 mg/kg to rat.
With higher doses, a linear increase in the amount opropranolol in blood is found (1004). Also, the first-pase
effe 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*-pro 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 u 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 al 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 (545). In addition, hepatic biotransformation of a parent
drug may produce metabolites that also undergo presys-
temic elimination. For example, approximately 90% of
monoethylglycine xylidide, a metabolite of lidocaine, i drug may produce metabolites that also undergo presys-
temic elimination. For example, approximately 90% of
monoethylglycine xylidide, a metabolite of lidocaine, is
extracted after a single pass through the liver (896), a temic 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, t beyonder the fluid of idocaine, is
tracted after a single pass through the liver (896), and
quential first-pass elimination of acetaminophen, the
retabolite of phenacetin, has been demonstrated (893).
The fractional uptak

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 wi 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 hy-
 metabolite of phenacetin, has been demonstrated (893).

The fractional uptake of insulin in man decreases with

increasing insulin dose and is lower during induced hy-

perglycemia than at fasting (1187). Results suggest The fractional uptake of insulin in man decreases w
increasing insulin dose and is lower during induced
perglycemia than at fasting (1187). Results suggest
patic uptake of insulin depends upon plasma gluc
concentrations. C The ractional update of insulin in main decreases with
increasing insulin dose and is lower during induced hy-
perglycemia than at fasting (1187). Results suggest he-
patic uptake of insulin depends upon plasma glucose
co highly dependent upon hepatic blood flow, although prepatic 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 pre-
sy concentrations. Clearance from blood of drugs administered systemically with significant first-pass effects is
highly dependent upon hepatic blood flow, although pre-
systemic extraction is independent of liver blood flow
 tered systemically with significant first-pass effect
highly dependent upon hepatic blood flow, although p
systemic extraction is independent of liver blood f
(850, 851, 894–896). For example, clearance of lidoca
in humans highly dependent upon hepatic blood flow, although pre-
systemic extraction is independent of liver blood flow
(850, 851, 894–896). For example, clearance of lidocaine
in humans was reduced after administration of proprano systemic extraction is independent of liver blood flow

(850, 851, 894–896). For example, clearance of lidocaine

in humans was reduced after administration of propran-

olol (860). Clearance and metabolism of propranolol (850, 851, 894–896). For example, clearance of lidocaine
in humans was reduced after administration of propran-
olol (860). Clearance and metabolism of propranolol and
reduction of indocyanine green were decreased by a 2 in humans was reduced after administration of propranciol (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 olol (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
 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-pas biphenyls enhances the intrinsic clearance and first-pass phenyls enhances the intrinsic clearance and first-pass
fect of pentobarbital in rats (1133). A pharmacokinetic
odel to differentiate preabsorptive, gut epithelial, and
patic first-pass metabolism has been described (205).

effect of pentobarbital in rats (1133). A pharmacokinetic model to differentiate preabsorptive, gut epithelial, and cle-
hepatic first-pass metabolism has been described (205). blow
Experiments to determine the effect of 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
per hepatic first-pass metabolism has been described (20
Experiments to determine the effect of presyste-
elimination on the toxicity of xenobiotics need to
performed. Existence of a first-pass effect would be
sirable for a no 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 de-
sirable for a non-therapeutic, toxic compound, prevent-
ing elimination on the toxicity of xenobiotics need to be
performed. Existence of a first-pass effect would be de-
sirable for a non-therapeutic, toxic compound, prevent-
ing its distribution to other parts of the body. Howeve performed. Existence of a first-pass effect would be de-
sirable for a non-therapeutic, toxic compound, prevent-
ing its distribution to other parts of the body. However,
in cases of decreased hepatic function, the chemica sirable 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 to ing its distribution to other parts of the body. However, 1000
in cases of decreased hepatic function, the chemical may 336 ,
escape the first-pass effect and produce a greater toxicity. Creatively
If the toxicant is b in cases of decreased hepatic function, the chemical may 33
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 escape the first-p
If the toxicant is
toxic metabolite
presystemic elim
chemical (640).
B. Henstic Clear 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 mical (640).

B. Hepatic Clearance

Clearance is a precise physiological measurement of red

the efficiency of xenobiotic elimination. This concept is sinclosely analogous to those in nephrology and provides a

eli dec
B. Hepatic Clearance
Clearance is a precise physiological measurement of
the efficiency of xenobiotic elimination. This concept is
sint closely analogous to those in nephrology and provides a
measure which changes line B. Hepatic Clearance
Clearance is a precise physiological measurement
the efficiency of xenobiotic elimination. This concept
closely analogous to those in nephrology and provides
measure which changes linearly with respect Clearance is a precise physiological measurement of reduced the efficiency of xenobiotic elimination. This concept is siclosely analogous to those in nephrology and provides a elemeasure which changes linearly with respect

D WATKINS
the efficiency of each route of elimination and does not
indicate the site or rate-limiting process. However, for D WATKINS
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 D WATKINS
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 the efficiency of each route of elimination and do
indicate the site or rate-limiting process. Howev
many chemicals, the liver is the major site of elimi
and systemic clearance reflects hepatic clearance.
Clearance is the e efficiency of each route of elimination and does not
dicate the site or rate-limiting process. However, for
any chemicals, the liver is the major site of elimination
d systemic clearance reflects hepatic clearance.
Clear

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,
 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, 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
 ratio (E_H) :

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

 $\text{Cl}_H = Q_H E_H = Q_H \left[\frac{C_a - C_c}{C_a} \right]$
where E_H is the arterial-venous concentration difference
across the liver, C_a is the concentration in mixed portal $Cl_H = Q_H E_H = Q_H \left[\frac{C_a - C_c}{C_a} \right]$
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 concen- $Cl_H = Q_H E_H = Q_H$
where E_H is the arterial-venous concentration different
across the liver, C_a is the concentration in mixed por
venous and hepatic arterial blood and C_v is the concentration in hepatic venous blood. Thus 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 concen-
tration in hepatic venous blood. Thus, hepat 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 concen-
tration in hepatic venous blood. Thus, hepat across the liver, C_a is the concentration in mixed portal
venous and hepatic arterial blood and C_v is the concen-
tration in hepatic venous blood. Thus, hepatic clearance
is a function of liver blood flow and the abil 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 t tration 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 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 use 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 irrevers 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 plas 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 pla 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, remove a chemical by all pathway
blood flow limitations. When the
membrane is highly permeable to E_H may be expressed in terms
 Cl_{INT} , (132, 389, 850) such that: Cl_{INT}, (132, 389, 850) such that:

$$
\text{Cl}_H = Q_H \cdot \frac{\text{Cl}_{\text{INT}}}{Q_H + \text{Cl}_{\text{INT}}}
$$

reduction in hepatic blood flow induced by cimetidine in blood flow are two independent biological variables which
humans (327). Short-term exposure to polychlorinated influence hepatic clearance and extraction. When intri $\text{Cl}_H = Q_H \cdot \frac{\text{Cl}_{\text{INT}}}{Q_H + \text{Cl}_{\text{INT}}}$
Physiologically, intrinsic clearance is an index of the
te at which a substance crosses the hepatic parenchy- $Cl_H = Q_H$ \bullet $\frac{Cl_{INT}}{Q_H + Cl_{INT}}$
Physiologically, intrinsic clearance is an index of rate at which a substance crosses the hepatic parenchy-
mal sinusoidal membrane. Intrinsic clearance and l $Cl_H = Q_H^*$ $\overline{Q_H + Cl_{INT}}$
Physiologically, intrinsic clearance is an index of the
rate at which a substance crosses the hepatic parenchy-
mal sinusoidal membrane. Intrinsic clearance and liver
blood flow are two independent Physiologically, intrinsic clearance is an index of the rate at which a substance crosses the hepatic parenchy-
mal sinusoidal membrane. Intrinsic clearance and liver
blood flow are two independent biological variables wh Physiologically, intrinsic clearance is an index of trate at which a substance crosses the hepatic parencher and sinusoidal membrane. Intrinsic clearance and livelod flow are two independent biological variables whis influ rate at which a substance crosses the hepatic parenchy-
mal sinusoidal membrane. Intrinsic clearance and liver
blood flow are two independent biological variables which
influence hepatic clearance and extraction. When intr mal sinusoidal membrane. Intrinsic clearance and liver
blood flow are two independent biological variables which
influence hepatic clearance and extraction. When intrin-
sic clearance is low, liver blood flow is adequate t blood flow are two independent biological variables which
influence hepatic clearance and extraction. When intrin-
sic clearance is low, liver blood flow is adequate to
maintain hepatic clearance at the same level as intri influence hepatic clearance and extraction. When intrinsic clearance is low, liver blood flow is adequate to maintain hepatic clearance at the same level as intrins clearance. If intrinsic clearance is high, then hepat blo maintain hepatic clearance at the same level as intrins
clearance. If intrinsic clearance is high, then hepat
blood flow becomes rate-limiting and total hepatic clear
ance varies in direct proportion to flow. Hepatic clear clearance. If intrinsic clearance Vietnam
blood flow becomes rate-li
ance varies in direct prop
ance is partly flow-depen
mediate intrinsic values.
Factors that cen alter h ood flow becomes rate-limiting and total hepatic clear
ce varies in direct proportion to flow. Hepatic clear
ce is partly flow-dependent for chemicals with inter-
ediate intrinsic values.
Factors that cen alter hepatic blo

presystemic elimination may increase the toxicity of the
cleared conditions, cardiovascular collapse, renal hypertension, and
congestive heart failure are pathological conditions that
decrease hepatic blood flow (1262). M ance varies in direct proportion to flow. Hepatic clear-
ance is partly flow-dependent for chemicals with inter-
mediate intrinsic values.
Factors that cen alter hepatic blood flow can be phys-
iological, pathological, and ance is partly flow-dependent for chemicals with inter-
mediate intrinsic values.
Factors that cen alter hepatic blood flow can be phys-
iological, pathological, and/or pharmacological (136, 137,
336, 850, 956, 957, 1261). mediate 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 Factors that cen alter hepatic blood flow can be phys-
iological, pathological, and/or pharmacological (136, 137,
336, 850, 956, 957, 1261). Physiological factors that de-
crease flow include upright posture, thermal stres iological, 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 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 ci crease flow include upright posture, thermal stress, ex-
ercise, (224) and volume depletion (476), while food and
supine posture increase hepatic blood flow. Hepatic cir-
rhosis, cardiovascular collapse, renal hypertension ercise, (224) and volume depletion (476), while food and
supine posture increase hepatic blood flow. Hepatic cir-
rhosis, cardiovascular collapse, renal hypertension, and
congestive heart failure are pathological condition supine posture increase hepatic blood flow. Hepatic cir-
rhosis, cardiovascular collapse, renal hypertension, and decrease hepatic blood flow (1262). Myocardial ischemia 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
 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
e produced by occlusion of coronary arteries causes a 6
reduction in hepatic blood flow (377). A diminish
sinusoidal perfusion may be responsible for the impain
elimination of propranolol observed in some patie
(923) and dur 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). Admin-
istra

aspet

BILE FORMATION, HEPATIC UPTAKE, AND BILIARY EXCRETION ¹⁹

eral anesthetics (449, 868, 1068) decrease hepatic blood BILE FORMATION, HEPATIC
eral anesthetics (449, 868, 1068) decrease hepatic blo
flow, while glucagon, isoproterenol, and repeated adm
istration of phenobarbital increase flow (867, 868). N BILE FORMATION, HEPATIC U
eral anesthetics (449, 868, 1068) decrease hepatic blood
flow, while glucagon, isoproterenol, and repeated admin
istration of phenobarbital increase flow (867, 868). Nor
mal hepatic perfusion in s eral anesthetics (449, 868, 1068) decrease hepatic blood
flow, while glucagon, isoproterenol, and repeated administration of phenobarbital increase flow (867, 868). Nor-
mal hepatic perfusion in several species, including eral anesthetics (449, 868, 1068) decrease hepatic blood chemid
flow, while glucagon, isoproterenol, and repeated admin-sic cle
istration of phenobarbital increase flow (867, 868). Nor-clearan
mal hepatic perfusion in seve flow, while glucagon, isoproterenol, and repeated admitstration of phenobarbital increase flow (867, 868). Not mal hepatic perfusion in several species, including matic 1 ml/min/g of liver (418, 1003). Hepatic blood flue istration of phenobarbital increase flow (867, 868). Nor-clear
mal hepatic perfusion in several species, including man, of c
is 1 ml/min/g of liver (418, 1003). Hepatic blood flow In a
determined under a variety of physiol mal hepatic perfusion in several species
is 1 ml/min/g of liver (418, 1003). He
determined under a variety of physiolo
logical conditions or after drug adminii
2.0 ml/min/g of liver (133, 224, 1134).
Blood concentration of 1 ml/min/g of liver (418, 1003). Hepatic blood flow
termined under a variety of physiological and patho-
gical conditions or after drug administration is 0.5 to
 $\ln |\min/g$ of liver (133, 224, 1134).
Blood concentration of a

determined under a variety of physiological and patho-
logical conditions or after drug administration is 0.5 to
2.0 ml/min/g of liver (133, 224, 1134). half
Blood concentration of a chemical after intravenous tive
and ora logical conditions or after drug administration is 0.5 to pound

2.0 ml/min/g of liver (133, 224, 1134). half-lif

Blood concentration of a chemical after intravenous tive to

and oral administration can be affected by a d 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 is
hepatic blood flow (1263). For a xenobiotic that has lovex
traction, syst Blood concentration of a chemical after intravenous tively and oral administration can be affected by a decrease in bidependent blood flow (1263). For a xenobiotic that has low oriextraction, systemic clearance and half-l and oral administration can be affected by a decrease if hepatic blood flow (1263). For a xenobiotic that has lovextraction, systemic clearance and half-life are flow
independent and the blood concentration/time curve is
s 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. How-
e 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. How-
ever, for a chemical with a high extraction, both clearanc independent and the blood concentration/time curve is depend
similar over a wide range of hepatic blood flows. How-
ever, for a chemical with a high extraction, both clearance
and half-life are flow-dependent after either similar over a wide range of hepatic blood flows. How-
ever, 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 fl ever, 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. Clear 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 extractio 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 build increase the half-life of the xenobiotic. Clearance intimediate extraction is dialy discussed the extraction ratio.

Alterations of intrinsic clearance can affect the blood is contrations of intrinsic clearance can a

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 ver 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 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 intri 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 en-
 concentration versus time curve of a xenobiotic af
intravenous and oral administration. The major effect
increasing intrinsic clearance as after microsomal extraction is a proportional increase in the e
ciency of hepatic e intravenous and oral administration. The major effect of increasing intrinsic clearance as after microsomal en-
zyme induction is a proportional increase in the effi-
ciency of hepatic extraction. The area under the concen increasing intrinsic clearance as after microsomal en
zyme induction is a proportional increase in the efficiency of hepatic extraction. The area under the concentration/time curve and half-life change in inverse pro
porti zyme 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 compoun ciency of hepatic extraction. The area under the concentration/time curve and half-life change in inverse pro-
portion to the change in intrinsic clearance. For a com-
pound with a low intrinsic clearance, a twofold increa tration/time curve and half-life change in inverse pro-
portion to the change in intrinsic clearance. For a com-
pound with a low intrinsic clearance, a twofold increase
in extraction would produce a 50% reduction in halfportion to the change in intrinsic clearance. For a con-
pound with a low intrinsic clearance, a twofold increas-
in extraction would produce a 50% reduction in half-lif-
However, systemic availability after oral administr pound 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 intrins However, systemic availability after oral administration
decreases only slightly. In contrast, when intrinsic clear-
ance is high, an increase in extraction produces minimal
alteration in clearance or half-life but markedl However, systemic availability after oral administration
decreases only slightly. In contrast, when intrinsic clear-
ance is high, an increase in extraction produces minimal
alteration in clearance or half-life but markedl decreases only slightly. In contrast, when intrinsic clear-
ance is high, an increase in extraction produces minimal
alteration in clearance or half-life but markedly increases
presystemic elimination after oral administra ance is high, an ince
alteration in cleara
presystemic elimin
blood levels are de
markedly reduced.
Large changes is Exercison in clearance or half-life but markedly increases
esystemic elimination after oral administration. Peak
ood levels are decreased and systemic availability is
bee
arkedly reduced.
Large changes in the rate of hepat

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 flo blood levels are decreased and systemic availabil
markedly reduced.
Large changes in the rate of hepatic perfusion
alter regional distribution of blood flow within he
lobes and influence the magnitude of bile acid-inde
ent 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-independ-
ent flow without significant changes in Large changes in the rate of hepatic perfusion may
alter regional distribution of blood flow within hepatic
plobes and influence the magnitude of bile acid-independ-
ent flow without significant changes in oxygen uptake,
 lobes and influence the magnitude of bile acid-independent flow without significant changes in oxygen uptake, aminotransferase release, $Na^+ \n-K^+ \nATP$ ase activity, or evidence of morphological damage (1164). Many in vivo t flow without significant changes in oxygen uptake,
ninotransferase release, Na⁺-K⁺-ATPase activity, or
idence of morphological damage (1164).
Many in vivo investigations demonstrating the effect
liver blood flow on s

aminotransferase release, Na^+K^+ATP ase activity,
evidence of morphological damage (1164).
Many in vivo investigations demonstrating the effect
of liver blood flow on systemic clearance and half-land the dependence of thi evidence of morphological damage (1164). We
Many in vivo investigations demonstrating the effect
of liver blood flow on systemic clearance and half-life
is and the dependence of this effect on the original extrac-
altion r 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 extrac-
ion ratio have been reviewed (1261). Studies in isolate of liver blood flow on systemic clearance and half-life
and the dependence of this effect on the original extrac-
tion ratio have been reviewed (1261). Studies in isolated
perfused rat liver also demonstrate interrelations and the dependence of this effect on the original extrac-
tion ratio have been reviewed (1261). Studies in isolated
perfused rat liver also demonstrate interrelationships of
the
extraction rate, liver blood flow rate, kin tion ratio have been reviewed (1261). Studies in isolated la
perfused rat liver also demonstrate interrelationships of the
xtraction rate, liver blood flow rate, kinetic elimination seconstants (K_m , V_{max}), and route o 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 cu 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 xenobioti constants (K_m, V_{max}) , and route of administration with potassium, is a concentrative process while that of tracer
respect to the blood concentration versus time curve glucose is non-concentrative. When intracellular seques **ratios have** definable differences in disposition. If a

KE, AND BILIARY EXCRETION
chemical has a low extraction ratio due to a small intr
sic clearance relative to liver blood flow, then hepa Since, AND BILIARY EXCRETION 19
Chemical has a low extraction ratio due to a small intrin-
sic clearance relative to liver blood flow, then hepatic
clearance and elimination half-life will be independent AKE, AND BILIARY EXCRETION 19

chemical has a low extraction ratio due to a small intrin

sic clearance relative to liver blood flow, then hepatic

clearance and elimination half-life will be independen

of changes in flow chemical has a low extraction ratio due to a small intrin
sic clearance relative to liver blood flow, then hepati
clearance and elimination half-life will be independen
of changes in flow but sensitive to hepatic metabolis chemical has a low extraction ratio due to a small intrin-
sic clearance relative to liver blood flow, then hepatic
clearance and elimination half-life will be independent
of changes in flow but sensitive to hepatic metabo 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 ad-
ministration will be observed. In contrast, for a c 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 ad-
ministration will be observed. In contrast, for a c of changes in flow but sensitive to hepatic metabolis In addition, only a small first-pass effect after oral ministration will be observed. In contrast, for a copound with a high extraction ratio, hepatic clearance and ins In addition, only a small first-pass effect after oral aministration will be observed. In contrast, for a conpound with a high extraction ratio, hepatic clearance an half-life will be sensitive to changes in flow and insen ministration 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 xen half-life will be sensitive to changes in flow and insensitive to alterations in metabolic activity. Such a xeno-
biotic will exhibit a significant first-pass effect after an
oral dose. Chemicals having intermediate extrac half-life will be sensitive to changes in flow and insensitive to alterations in metabolic activity. Such a xeno-
biotic will exhibit a significant first-pass effect after an
oral dose. Chemicals having intermediate extrac tive to alterations in metabolic activity. Such a xen
biotic will exhibit a significant first-pass effect after
oral dose. Chemicals having intermediate extraction
tios have mixed properties, in that clearance is part
depe From the extrict a signal dose. Chemicals have mixed properties a signal dose in the properties of the *C. Hepatic Uptake*
C. Hepatic Uptake
Before a solute loc. **Before a solute properties, in that clearance is partly pendent on liver blood flow and hepatic metabolism.**
 Before a solute located in sinusoidal blood can be corporated into the parenchymal cell, the compound

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 s C. Hepatic Uptake
Before a solute located in sinusoidal blood can
incorporated into the parenchymal cell, the compou
must pass through fenestrations of the sinusoidal epith
lia and enter the space of Disse (see fig. 2). Th 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 epithe-
lia and enter the space of Disse (see fig. Before a solute located in sinusoidal blood can be
incorporated into the parenchymal cell, the compound
must pass through fenestrations of the sinusoidal epithe-
lia and enter the space of Disse (see fig. 2). Then the
solu incorporated into the parenchymal cell, the compo
must pass through fenestrations of the sinusoidal epi
lia and enter the space of Disse (see fig. 2). Then
solute contacts the microvilli of the plasma memb
and uptake occur must pass through fenestrations of the sinusoidal epith
lia and enter the space of Disse (see fig. 2). Then the
solute contacts the microvilli of the plasma membrar
and uptake occurs. Besides these structural consider
tion lia 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 determina solute contacts the microvilli of the plasma membrane
and uptake occurs. Besides these structural considera-
tions, the velocity of blood flow is an important deter-
minant of the probability of interaction between solute
 d uptake occurs. Besides these structural consider has, the velocity of blood flow is an important detainant of the probability of interaction between solud microvilli.
The uptake of substances by the liver has been examed

tions, the velocity of blood flow is an important deter-
minant of the probability of interaction between solute
and microvilli.
The uptake of substances by the liver has been exam-
ined by several methods: 1) determinatio 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 plasm The uptake of substances by the liver has been exam-
ined 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 ined 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 st 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 concentratio 2) study of the partition between plasma and liver ce
after infusion for a sufficient time to achieve a stead
state; 3) quantification of the hepatic concentration
various times; 4) examination of the ability of the isolat 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 perfusate; 5) determination of the ability of i 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 perfu-
sate; 5) determination of the ability of isolat various times; 4) examination of the ability of the isolated
perfused liver to concentrate a chemical from the perfu-
sate; 5) determination of the ability of isolated or cul-
tured hepatocytes to accumulate a chemical fro perfused liver to concentrate
sate; 5) determination of th
tured hepatocytes to accum
medium; and 6) measureme
isolated membrane vesicles.
Two methods for the stu te; 5) determination of the ability of isolated or cul-
red hepatocytes to accumulate a chemical from the
edium; and 6) measurement of xenobiotic influx into
blated membrane vesicles.
Two methods for the study of hepatic u

lobes and influence the magnitude of bile acid-independ-
ent flow without significant changes in oxygen uptake,
aminotransferase release, Na⁺-K⁺-ATPase activity, or
aminotransferase release, Na⁺-K⁺-ATPase activity tured 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 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) 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 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 $(40$ 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 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 pro-
files consist of a throughput component which does study uptake of chemicals at the liver cell surface (401) .
This process (fig. 6) has been modeled and outflow pro-
files consist of a throughput component which does not
enter the liver (${}^{51}Cr$ -labeled red blood cells This process (fig. 6) has been modeled and outflow pro-
files consist of a throughput component which does not
enter the liver (5^1 Cr-labeled red blood cells or albumin
labeled with Evans blue dye) and a return componen enter the liver (⁵¹Cr-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 proc 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 larged cellular volume. In a non-concentrative process is concentrative, the throughput component emerges well ahead of the returning component by virtue of the en-
larged cellular volume. In a non-concentrative process,
t is concentrative, the throughput component emerges well
ahead of the returning component by virtue of the en-
larged cellular volume. In a non-concentrative process,
the throughput and returning components are not widely
s ahead of the returning component by virtue of the en-
larged cellular volume. In a non-concentrative process,
the throughput and returning components are not widely
separated in time. The uptake of tracer rubidium, like
po larged cellular volume. In a non-concentrative proce
the throughput and returning components are not wid
separated in time. The uptake of tracer rubidium, li
potassium, is a concentrative process while that of traa
glucose 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 seques-
tration occurs, the magnitude of the returning compo-
nent in a tracer experiment is reduced and a decreas glucose is non-concentrative. When intracellular sequesglucose is non-concentrative. When intracellular seques-
tration occurs, the magnitude of the returning compo-
nent in a tracer experiment is reduced and a decreasing
steady state lobular gradient is produced from the peri

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0 10 20 30 40
 SECONDS

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 **SECONDS**
FIG. 6. In vivo multiple indicator dilution technique adapted to study uptake of chemicals at liver cell at
throughput component which enters the liver cell and returns to the plasma space to emerge at the outflo FIG. 6. In vivo multiple indicator dilution technique adapted to sthroughput component which does not enter the liver (⁵¹Cr-labeled recomponent which enters the liver cell and returns to the plasma space to ing component dy uptake of chemicals at liver cell surface. Outflow profiles are a
blood cells or albumin labeled with Evans blue dye) and a return
emerge at the outflow (tritiated water).
in the rat in vivo, in isolated perfused liver,

throughput component which does not enter the liver $(^{61}Cr$ -labeled component which enters the liver cell and returns to the plasma space ing components has been observed for galactose, BSP bilirubin, cholate, taurochola ing components has been observed for galactose, BSP, in bilirubin, cholate, taurocholate, and chenodeoxycholate is (401, 967). While this technique has been useful, it is invery labor intensive, and thus most of the work p ing components has been observed for gala
bilirubin, cholate, taurocholate, and chenod
(401, 967). While this technique has been
very labor intensive, and thus most of the wo
being performed is with isolated hepatocytes
Su

(401, 967). While this technique has been useful, it is in very labor intensive, and thus most of the work presently useing performed is with isolated hepatocytes. In Suspensions of hepatocytes isolated by the method of i very labor intensive, and thus most of the work presently up
being performed is with isolated hepatocytes. is
Suspensions of hepatocytes isolated by the method of
is
Berry and Friend (98) are particularly advantageous for
 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 (6 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
all Berry and Friend (98) are particularly advantageous fo
examining the characteristics of the hepatic uptake o
chemicals (666, 1053). Isolated hepatocyte suspension
allow rapid, multiple sampling which permits estimation
of 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 paramet chemicals (666, 1053). Isolated hepatocyte suspensions in allow rapid, multiple sampling which permits estimation pof initial velocities and calculation of kinetic parameters. ce These cells are useful for studying uptake 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 bin ments or hemodynamic factors. However, workers must
demonstrate that cell viability is high and maintained These cells are useful for studying uptake processes
because there is no interference from unspecific binding
to plasma proteins, different distributional compart-
ments or hemodynamic factors. However, workers must
demons because there is no interference from unspecific binding
to plasma proteins, different distributional compart-
ments or hemodynamic factors. However, workers must
demonstrate that cell viability is high and maintained
thro to plasma proteins, different distributional compart-
ments or hemodynamic factors. However, workers must live
demonstrate that cell viability is high and maintained sc
throughout the study. Transport characteristics of se ments or hemodynamic factors. However, workers must
demonstrate that cell viability is high and maintained
throughout the study. Transport characteristics of sev-
eral classes of compounds have been tabulated recently
(105 demonstrate that cell viability is high and mainta
throughout the study. Transport characteristics of
eral classes of compounds have been tabulated rece
(1057) which include bile acids (38, 39, 529, 1051),
bain (284), proc eral classes of compounds have been tabulated recently (1057) which include bile acids (38, 39, 529, 1051), oua-
bain (284), procainamide ethobromide (285), 3-O-meth-
ylglucose, D-fructose, and D-galactose (221, 222), morylglucose, D-fructose, and D-galactose (221, 222), mor-(1057) which include bile acids (38, 39, 529, 1051), oua-
bain (284), procainamide ethobromide (285), 3-O-meth-
ylglucose, D-fructose, and D-galactose (221, 222), mor-
phine and nalorphine (541), BSP (1058, 1059), BSP-
gl bain (284), procainamide ethobromide (285), 3-O-meth-
ylglucose, D-fructose, and D-galactose (221, 222), mor-
phine and nalorphine (541), BSP (1058, 1059), BSP-
glutathione (1053), insulin (1171), thiamine (755), bili-
rub ylglucose, D-fructose, and D-galactose (221, 222), morphine and nalorphine (541), BSP (1058, 1059), BSP-
glutathione (1053), insulin (1171), thiamine (755), bili-
rubin (525), parathion (838), lipoproteins (886, 1199),
iro phine and nalorphine (541), BSP (1058, 1059), BSP-
glutathione (1053), insulin (1171), thiamine (755), bili-
rubin (525), parathion (838), lipoproteins (886, 1199),
iron (434, 435), zinc (1121), cadmium (320–322, 1119),
es glutathione (1053), insulin (1171), thiamine (755), bili-

rubin (525), parathion (838), lipoproteins (886, 1199), cl

iron (434, 435), zinc (1121), cadmium (320–322, 1119), bi

estrogens (1060), taurine (464), alanine (68 rubin (525), parathion (838), lipoproteins (886, 1199), cho
iron (434, 435), zinc (1121), cadmium (320–322, 1119), bile
estrogens (1060), taurine (464), alanine (687), and other one
amino acids (175, 292, 328, 571, 721, 72 estrogens (1060), taurine (464), alanine (687), and other or amino acids (175, 292, 328, 571, 721, 722). The majority bot these organic compounds appear to be taken up by a recarrier-mediated system while lipophilic xenobi estrogens (1060), taurine (464), alanine (687), and othe
amino acids (175, 292, 328, 571, 721, 722). The majorit
of these organic compounds appear to be taken up by
carrier-mediated system while lipophilic xenobiotics ma
p of these organic compounds appear to be taken up by a

carrier-mediated system while lipophilic xenobiotics may

tal

pass through the membrane by diffusion (1057). Lido-

caine uptake is not carrier-mediated, and binding carrier-mediated system wh
pass through the membran
caine uptake is not carrie
intracellular components m
tion in hepatocytes (176).
Recently, hepatic trans as through the membrane by diffusion (1057). Lido
ine uptake is not carrier-mediated, and binding to
tracellular components may account for its accumula
in in hepatocytes (176).
Recently, hepatic transport of three xenobio caine uptake is not carrier-mediated, and binding to Sintracellular components may account for its accumula-
tion in hepatocytes (176).
Recently, hepatic transport of three xenobiotics, b
DBSP, *d*-tubocurarine and ouabai

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, in the rat in vivo, in isolated perfused liver, and in (401, 967). While this technique has been useful, it is in the perfused liver for all three substrates. However, very labor intensive, and thus most of the work presently uptake of DBSP and ouabain into isolated hepatocyt isolated hepatocytes (116). Uptake is similar in vivo and a return
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 substr 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 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 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 hepatocy in the perfused liver for all three substrates. However, identical for DBSP and lower for ouabain and d-tubouptake 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 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*-tubo-
curarine than that of the in vivo preparatio is similar. Rate of secretion from isolated hepatocytes is
identical for DBSP and lower for ouabain and d -tubo-
curarine than that of the in vivo preparation. Results
indicate that transport function is well preserved i curarine 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 i curarine than that of the in vivo prepaindicate that transport function is we perfused livers and isolated hepatocyte certain substrates, uptake and/or secretion freshly isolated cells of high viability.
1. Bile Acids. Hep dicate that transport function is well preserved in rfused livers and isolated hepatocytes although, for train substrates, uptake and/or secretion may be lower freshly isolated cells of high viability.
1. *Bile Acids*. Hep 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 20 30 30 40
 ± 20 30 30 40 5
 ± 20 30 30 40
 ± 20 and ± 20
 ± 2

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 (9 in freshly isolated cells of high viability.

1. Bile Acids. Hepatocellular uptake of taurocholi

appears to be saturable in dogs (393) and perfuse

liver (967). This carrier-mediated transport syst

sodium-dependent (114, 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-dep 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-depend-
ent (1051). Uptake of cholate occurs apparently by both
sim liver (967). This carrier-mediated transport system
sodium-dependent (114, 967, 1051) and energy-depen
ent (1051). Uptake of cholate occurs apparently by bo
simple diffusion and a saturable process and undergo
counter-tran sodium-dependent (114, 967, 1051) and energy-deper
ent (1051). Uptake of cholate occurs apparently by bo
simple diffusion and a saturable process and underg
counter-transport (188) with taurocholate and cher
deoxycholate (simple diffusion and a saturable process and undergoes
counter-transport (188) with taurocholate and cheno-
deoxycholate (39). Transport of cholate appears concen-
trative in nature but is complicated by conjugation with
g counter-transport (188) with taurocholate and chen
deoxycholate (39). Transport of cholate appears conce
trative in nature but is complicated by conjugation wi
glycine or taurine and protein binding. The relati
potencies o deoxycholate (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 tauroc trative 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 tauro-
cholate uptake suggest several carriers are available glycine or taurine and protein binding. The relative potencies of seven bile acids to inhibit cholate or tauro-
cholate uptake suggest several carriers are available for
bile acid uptake which may have affinity for more th potencies of seven bile acids to inhibit cholate or tauro-
cholate 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 e cholate 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/ 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 taurocholat between cholate and taurocholate (13.3 and 29 Kcal/mol,
respectively) and selective inhibition of taurocholate up-
take by ouabain further suggest that multiple carriers
are involved in bile acid transport into the hepatoc 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 take 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) 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 fr 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).

PHARMACOLOGICAL REVIEWS

bile acid uptake than periportal cells (1120). While the depends on binding to both albumin (69) and intracel-
K_n of each subpopulation was the same, the V_{nex} of the lular binding proteins such as ligandin (728). BILE FORMATION, HEPATIC UPTAKI
Centrilobular hepatocytes have a higher capacity for nis
bile acid uptake than periportal cells (1120). While the de
K_m of each subpopulation was the same, the V_{max} of the lul BILE FORMATION, HEPATIC UPTAKI
Centrilobular hepatocytes have a higher capacity for nis
bile acid uptake than periportal cells (1120). While the de
K_m of each subpopulation was the same, the V_{max} of the lul
centrilobu 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 Centrilobular hepatocytes have a higher capacity for nivel and the diverse and that of the same, the V_{max} of the lucentrilobular enriched fraction was 2.03 nmol/min/mg of protein and that of the periportal-enriched frac bile acid up
 K_m of each
centrilobula
of protein
was 1.57.
The hep 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 8

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 8 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 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 hy The hepatic extraction of taurocholic, glycocolic, lecholic, deoxycholic, and chenodeoxycholic acids is 80%, 65%, 55%, 55%, and 40%, respectively, indicating that conjugation is more important than the number of hy-idroxy cholic, deoxycholic, and chenodeoxycholic acids is 80%, wit
65%, 55%, 55%, and 40%, respectively, indicating that μ M
conjugation is more important than the number of hy-
itoryl groups for bile acids to be removed by th 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 aci conjugation is more important than the number of hy-
droxyl groups for bile acids to be removed by the liver
(495, 528). Studies determining K_m and V_{max} for bile acid
were into isolated hepatocytes demonstrate that co droxyl 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 con-
jugation with taurine increases the affinity of (495, 528). Studies determining K_m and V_{max} for bile actuptake into isolated hepatocytes demonstrate that conjugation with taurine increases the affinity of the biacid for its transport carrier. In contrast, conjugati uptake into isolated hepatocytes demonstrate that co
jugation with taurine increases the affinity of the bi
acid for its transport carrier. In contrast, conjugation
with glycine did not affect either V_{max} or K_m . The t jugation with taurine increases the affinity of the bile traced for its transport carrier. In contrast, conjugation appoint glycine did not affect either V_{max} or K_m . The trihy-
droxy bile acids have a higher affinity acid for its transport carrier. In contrast, conjugation
with glycine did not affect either V_{max} or K_m . The trihy-
droxy bile acids have a higher affinity but a lower trans-
porting capacity for the saturable processe with glycine did not affect either V_{max} or K_m . The trihy-
droxy bile acids have a higher affinity but a lower trans-
porting capacity for the saturable processes than the
dihydroxy bile acids. In vivo hepatic extracti droxy bile acids have a higher affinity but a lower trans-
porting capacity for the saturable processes than the 3
dihydroxy bile acids. In vivo hepatic extraction appears she
to be more dependent on the affinity of the b porting capacity fo
dihydroxy bile acids
to be more depender
the carrier system t
transported (592).
Uptake of taurocl hydroxy bile acids. In vivo hepatic extraction appears she more dependent on the affinity of the bile acids for tre carrier system than the capacity at which it can be behapported (592).
Uptake of taurocholate into culture

to be more dependent on the affinity of the bile aci
the carrier system than the capacity at which it c
transported (592).
Uptake of taurocholate into cultured hepatocyte
also been shown to be transported by an energy-de
e the carrier system than the capacity at which it can transported (592).
Uptake of taurocholate into cultured hepatocytes
also been shown to be transported by an energy-depent, saturable system (1050, 1051) that is sodium
p s a subsety of taurocholate into cultured hepatocytes has belse of taurocholate into cultured hepatocytes has also been shown to be transported by an energy-depend-
ent, saturable system (1050, 1051) that is sodium-de-
pen Uptake of taurocholate into cultured hepatocytes has
also been shown to be transported by an energy-depend-
ent, saturable system $(1050, 1051)$ that is sodium-de-
pendent (1036) . Similar results were recently observed
 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). ent, saturable system (1050, 1051) that is sodium-de-
pendent (1036). Similar results were recently observed up
with isolated rat liver plasma membrane vesicles (538, in
1014). Sodium ion-coupled uptake was inhibited by ot pendent (1036). Similar results were recently observed up
with isolated rat liver plasma membrane vesicles (538, inc
1014). Sodium ion-coupled uptake was inhibited by other by
bile acids and by preloading the vesicles wit 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 stim Na⁺-dependent taurocholate transport. bile acids and by preloading the vesicles with Na^+ . When bile acids (707). Taurocholate inhibition reveals a bile-
the electrical potential difference was changed by anion acid-sensitive carrier with a 10-fold higher af 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 ph

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), suggesti Na⁺-dependent taurocholate transport.
Additional studies indicate that bile acids inhibit the
uptake of phallotoxins into isolated hepatocytes (36
917), suggesting phalloidin and demethylphalloin ent
the hepatocyte via t Additional studies indicate that bile acids inhibit the
uptake of phallotoxins into isolated hepatocytes (366, st
917), suggesting phalloidin and demethylphalloin enter list
the hepatocyte via the bile acid carrier. Pretre uptake of phallotoxins into isolated hepatocytes $(366, 917)$, suggesting phalloidin and demethylphalloin enter l
the hepatocyte via the bile acid carrier. Pretreatment by
with numerous xenobiotics reduces the sensitivity 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. Conflic with numerous xenobiotics reduces the sensitivity of

isolated hepatocytes to phalloidin probably by inhibiting λ
hepatic uptake of the toxin (918).
2. Bilirubin. Conflicting evidence exists on the cellular p
mechanism of bilirubin uptake. Over a wide range of a
plasma co approaches 26% with the toxin (918). The cellular and the cellular perchanism of bilirubin uptake. Over a wide range of a plasma concentrations, hepatic extraction of bilirubin wapproaches 26% with little change in bile fl 2. Bilirubin. Conflicting evidence exists on the cellular perchanism of bilirubin uptake. Over a wide range of a plasma concentrations, hepatic extraction of bilirubin wapproaches 26% with little change in bile flow or 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 approaches 26% with little change in bile flow or bilirubin cate that DBSP uptake also occurs against an electro-
conjugation. However, when bolus injections of bilirubin chemical gradient and utilizes the sodium ion-depen approaches 26% with little change in bile flow or bilirubin conjugation. However, when bolus injections of bilirubin cluster were used to produce higher levels of unconjugated bilicarity when in the perfusate than could be conjugation. However, when bolus injections of bilirubin correct used to produce higher levels of unconjugated bili-
rubin in the perfusate than could be attained during unconstant infusion, the disappearance rate of bilir were used to produce higher levels of unconjugated bili-
rubin in the perfusate than could be attained during
constant infusion, the disappearance rate of bilirubin
from the perfusate decreases with increasing bilirubin
co rubin 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
pr constant infusion, the disappearance rate of bilirul
from the perfusate decreases with increasing bilirul
concentrations. These data suggest uptake is a satural
process (119, 903). Other data indicate that deoxychola
inhib 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). concentrations. These data suggest uptake is a saturable aprocess (119, 903). Other data indicate that deoxycholate pinhibits bilirubin clearance from the plasma (118). More-
inhibits bilirubin uptake can be defined in ter process (119, 903). Other data indicate that deoxychola
inhibits bilirubin clearance from the plasma (118). Mo
over, bilirubin uptake can be defined in terms of N
chaelis-Menten kinetics and is competitively inhibit
by ind inhibits bilirubin clearance from the plasma (118). More-BS
over, bilirubin uptake can be defined in terms of Mi-
chaelis-Menten kinetics and is competitively inhibited
by indocyanine green and BSP (1038) but not by tauroover, bilirubin uptake can be defined in terms of N
chaelis-Menten kinetics and is competitively inhibit
by indocyanine green and BSP (1038) but not by tau
cholate (903). These data indicate that bilirubin is
likely substr

BILE FORMATION, HEPATIC UPTAKE, AND BILIARY EXCRETION **BILIARY EXCRETION** 21
Centrilobular hepatocytes have a higher capacity for nism. However, other studies report bilirubin clearance KE, AND BILIARY EXCRETION 21
nism. However, other studies report bilirubin clearance
depends on binding to both albumin (69) and intracel-KE, AND BILIARY EXCRETION
nism. However, other studies report bilirubin cleara
depends on binding to both albumin (69) and intrac
lular binding proteins such as ligandin (728). KE, AND BILIARY EXCRETION
nism. However, other studies report bilirubin
depends on binding to both albumin (69) and
lular binding proteins such as ligandin (728).
In isolated hepatocytes, uptake is extremely Im a However, other studies report bilirubin clearance
pends on binding to both albumin (69) and intracel-
ar binding proteins such as ligandin (728).
In isolated hepatocytes, uptake is extremely rapid and
uilibrium betwee

nism. However, other studies report bilirubin clearance
depends on binding to both albumin (69) and intracel-
lular binding proteins such as ligandin (728).
In isolated hepatocytes, uptake is extremely rapid and
equilibriu depends on binding to both albumin (69) and intracel-
lular binding proteins such as ligandin (728).
In isolated hepatocytes, uptake is extremely rapid and
equilibrium between cell and medium is attained within
60 seconds hepatocytes, uptake is extremely rapid and
initial velocity of 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). 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 lin equilibrium between cell and medium is attained with
50 seconds with a 100-fold greater concentration in the
patocyte (525). The initial velocity of uptake is line
with respect to bilirubin concentration from 12.5 to 2
 μ 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 μ M. Pretreatment of cells with various metabol hepatocyte (525). The initial velocity of uptake is linear
with respect to bilirubin concentration from 12.5 to 200
 μ M. Pretreatment of cells with various metabolic inhib-
itors or replacement of sodium ion with cholin with respect to bilirubin concentration from 12.5 to 200 μ M. Pretreatment of cells with various metabolic inhibitors or replacement of sodium ion with choline or lithium ion had no effect on bilirubin uptake. Accumulat μ M. Pretreatment of cells with various metabolic is
itors or replacement of sodium ion with choline or
ium ion had no effect on bilirubin uptake. Accumu
was not inhibited by the inclusion of organic acids
or taurochola itors or replacement of sodium ion with choline or lith-
ium ion had no effect on bilirubin uptake. Accumulation
was not inhibited by the inclusion of organic acids (BSP
or taurocholate) or steroidal compounds (diethylstil ium ion had no effect on bilirubin uptake. Accumulation
was not inhibited by the inclusion of organic acids (BSP
or taurocholate) or steroidal compounds (diethylstilbes-
trol or spironolactone). This study suggests that bi was not inhibited by the inclusion of organic acids (BSP
or taurocholate) or steroidal compounds (diethylstilbes-
trol or spironolactone). This study suggests that bilirubin
apparently reaches the cytoplasm simply by passi for taurocholate) or steroidal compounds (dieth
trol or spironolactone). This study suggests that
apparently reaches the cytoplasm simply by pa
fusion; however, the high accumulation probat
from association with intracellu be of spironolactone). This study suggests that bilirubin
parently reaches the cytoplasm simply by passive dif-
sion; however, the high accumulation probably results
om association with intracellular constituents.
3. Exoge sheep with reaches the cytoplasm simply by passive chase of the fight of the high accumulation probably resultion association with intracellular constituents.

3. Exogenous Organic Anions. Mutant Southdo sheep with normal

fusion; 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 concen-
trate other o from association with intracellular constituents.

3. Exogenous Organic Anions. Mutant Southdown

sheep with normal bile acid uptake are unable to concen-

trate other organic anions such as BSP, bilirubin, rose

bengal, a 3. Exogenous Organic Anions. Mutant Southdown
sheep with normal bile acid uptake are unable to concen-
trate other organic anions such as BSP, bilirubin, rose
bengal, and indocyanine green (217). This evidence of
separate sheep with normal bile acid uptake are unable to conductrate other organic anions such as BSP, bilirubin, if being being being being the observation that taurocho-
separate carrier systems for organic anionic dyes bile aci trate 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 taurocho-
 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 dy separate carrier systems for organic anionic dyes and
bile acids is supported by the observation that taurocho-
late does not inhibit BSP uptake (1059, 1212). At lower
dye concentrations, however, taurocholate can inhibit
 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 indi late 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 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 ac 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-
aci by rat hepatocytes and that one carrier is shared with the Na⁺-independent carrier of bile acids (38).

isolated hepatocytes to phalloidin probably by inhibiting Menten kinetics only at low substrate concentrations
hepatic uptake of the toxin (918).
2. Bilirubin. Conflicting evidence exists on the cellular port. Taurocholat Bilirubin, BSP, and indocyanine green are competitive acid-sensitive carrier with a 10-fold higher affinity
BSP than that of the insensitive one, which is proba
the Na⁺-independent carrier of bile acids (38).
Bilirubin, BSP, and indocyanine green are competit
substrates 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 Michae-
lis-Me the Na⁺-independent carrier of bile acids (38).

Bilirubin, BSP, and indocyanine green are competitive

substrates for a transport system which follows Michae-

lis-Menten kinetics (400, 1038). Similar results have

been Bilirubin, BSP, and indocyanine green are competisubstrates for a transport system which follows Michaelis-Menten kinetics (400, 1038). Similar results been obtained with isolated hepatocytes (1058, 11200). BSP uptake in i 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 been obtained with isolated hepatocytes (1058, 1127, 1200). BSP uptake in isolated cells follows Michaelis-Menten kinetics only at low substrate concentrations Menten kinetics only at low substrate concentrations
and is independent of metabolic energy and Na⁺ trans
port. Taurocholate does not affect uptake while indocy
anine green inhibits at low concentrations and activates
w and is independent of metabolic energy and Na⁺ tranception. Taurocholate does not affect uptake while indo
anine green inhibits at low concentrations and active
when BSP is greater than 20 μ M. Similar findings in
cat port. Taurocholate does not affect uptake while indocution
anine green inhibits at low concentrations and activate
when BSP is greater than 20 μ M. Similar findings ind
cate that DBSP uptake also occurs against an elect when BSP is greater than 20 μ M. Similar findings indiwhen BSP is greater than 20 μ M. Similar findings indicate that DBSP uptake also occurs against an electro-
chemical gradient and utilizes the sodium ion-dependent
carrier (115). Recent work indicates that the hepatic
u cate that DBSP uptake also occurs against an electr
chemical gradient and utilizes the sodium ion-depende
carrier (115). Recent work indicates that the hepat
uptake of BSP-glutathione is substantially lower that
that of BS chemical 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 trans-
port 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 com uptake of BSP-glutathione is substantially lower than
that of BSP, but both compounds share a common trans-
port mechanism (1052). Hepatocytes with poor viability,
as compared to high viability cells, have different kineti that of BSP, but both compounds share a common trans-
port mechanism (1052). Hepatocytes with poor viability,
as compared to high viability cells, have different kinetic
properties for BSP uptake which suggests that the lo port 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 l compared to high viability cells, have different kinetic
operties for BSP uptake which suggests that the lower
SP clearance observed in patients with impaired liver
nction may be due to depressed uptake (1059).
Rifamycins, BSP clearance observed in patients with impaired liver
function may be due to depressed uptake (1059).
Rifamycins, broad-spectrum antibiotics with low tox-
icity, interfere with the elimination of bilirubin, BSP,

BSP clearance observed in patients with impaired liver
function may be due to depressed uptake (1059).
Rifamycins, broad-spectrum antibiotics with low tox-
icity, interfere with the elimination of bilirubin, BSP,
and indoc function may be due to depressed uptake (1059).

Rifamycins, broad-spectrum antibiotics with low tox-

icity, interfere with the elimination of bilirubin, BSP,

and indocyanine green in humans (12) and with hepatic

uptake ²²
(600) in rats. In addition, hepatic transport of tauroc
late is inhibited by rifamycin SV in isolated perfused EXTERN AN

1922 KLAASSEN AN

1930) in rats. In addition, hepatic transport of taurocho-

1941 late is inhibited by rifamycin SV in isolated perfused rat

1941 liver (688, 689). These antibiotics inhibit cholate uptake kLAASSEN AND
(600) in rats. In addition, hepatic transport of taurocho-
late is inhibited by rifamycin SV in isolated perfused rat
liver (688, 689). These antibiotics inhibit cholate uptake
into isolated hepatocytes more t (600) in rats. In addition, hepatic transport of taurocho-
late is inhibited by rifamycin SV in isolated perfused rat $\frac{1}{2}$
liver (688, 689). These antibiotics inhibit cholate uptake $\frac{1}{2}$
into isolated hepatocyte (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 taurochola late is inhibited by rifamycin SV in isolated perfused r
liver (688, 689). These antibiotics inhibit cholate uptal
into isolated hepatocytes more than taurocholate uptal
and the inhibition appears to be non-competitive (41 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 sat into isolated hepatocytes more than taurocholate uptake graded the inhibition appears to be non-competitive (41). mat
Furthermore, hepatocyte uptake of rifamycin is a satur-
to be carrier-mediated process independent of me and the inhibition appears to be non-competitive (41
Furthermore, hepatocyte uptake of rifamycin is a satu
able carrier-mediated process independent of metabol
energy and is not inhibited by BSP. However, BS
uptake is comp in the carrier-mediated process independent of metabolic tionarier-mediated process independent of metabolic tionary and is not inhibited by BSP. However, BSP and take is competitively inhibited by rifamycin (703). is is i

able 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 a energy and is not inhibited by BSP. However, BS
uptake is competitively inhibited by rifamycin (703).
Biliary contrast agents are specifically taken up by tl
liver and are actively secreted into bile. Uptake into r
liver s 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-satur Biliary contrast agents are specifically taken up by the

liver and are actively secreted into bile. Uptake into rat

shiver slices is biphasic and consists of a non-saturable,

low affinity system and a saturable, high af liver and are actively secreted into bile. Uptake into rat sliver slices is biphasic and consists of a non-saturable, low affinity system and a saturable, high affinity carrier gent for that may be energy dependent. Inhibi 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 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,
1 that may be energy dependent. Inhibition of uptake is by apparently influenced by the affinity of the agent for in plasma albumin (95-97, 741, 749, 750, 819, 822, 823, is 1112). Uptake of ethacrynic acid into the isolated 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
par 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 extracel 1112). Uptake of ethacrynic activer is mediated by a saturable
partially Na⁺-dependent transportially Na⁺-dependent transportially of uptake can be increasible.
hular Na⁺ concentration (908).
An energy-dependent and er is mediated by a saturable, energy-dependent, a
rtially Na⁺-dependent transport mechanism. Maxin
locity of uptake can be increased by raising extrac
lar Na⁺ concentration (908).
An energy-dependent and saturable sys

partially Na⁺-dependent transport mechanism. Maximal
velocity of uptake can be increased by raising extracel-
lular Na⁺ concentration (908).
An energy-dependent and saturable system is respon-
sible for the rapid uptak velocity of uptake can be increased by raising extracel-

lular Na⁺ concentration (908). Studies in the new studies of warfarin but not dicoumarol studies

sible for the rapid uptake of warfarin but not dicoumarol studie been shown for the rend of 908).

An energy-dependent and saturable system is respon-

sible for the rapid uptake of warfarin but not dicoumarol

(1285). A saturable, active transport system has also

ne shown for both up An energy-dependent and saturable system is resp
sible for the rapid uptake of warfarin but not dicoum.
(1285). A saturable, active transport system has a
been shown for both uptake and biliary excretior
orotate which is sible 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 -amino-hi been shown for both uptake and biliary excretion of orotate which is inhibited by probenecid and p -amino-hippurate (459). Thus, the hepatic uptake of several exogenous anions appears to occur by a carrier-mediated trans been shown for both uptake and biliary excretion of Hepatic uptake for ouabain has been studied in detail
orotate which is inhibited by probenecid and p-amino-
in isolated hepatocytes (284, 1061). Uptake is saturable,
hip orotate which is inhibited by probenecid and p -amino-
hippurate (459). Thus, the hepatic uptake of several wexogenous anions appears to occur by a carrier-mediated p
transport system distinct from that of bile acids, bu hippurate (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 amination. ansport system distinct from that of bile acids, but the umber of transport systems and their specificity for take of exogenous organic anions requires further ex-
innation.
4. *Exogenous Organic Cations*. Rat liver has an number of transport systems and their specificity for
uptake of exogenous organic anions requires further ex-
amination.
4. Exogenous Organic Cations. Rat liver has an efficient
system for uptake and biliary excretion of q

uptake of exogenous organic anions requires further ex
amination.
4. Exogenous Organic Cations. Rat liver has an efficien
system for uptake and biliary excretion of quaternary
(486, 1031) and tertiary (839) ammonium compou amination.

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, o 4. Exogenous Organic Cations. Rat liver has an efficient in system for uptake and biliary excretion of quaternary c (486, 1031) and tertiary (839) ammonium compounds. 6 Uptake is not inhibited by bile acids, BSP, or probe system for uptake and biliary excretion of quaternary creaders (486, 1031) and tertiary (839) ammonium compounds. 6. C Uptake is not inhibited by bile acids, BSP, or probenecid dier (524, 1031). Procainamide ethobromide (P (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
omi 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 inh (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). Be-
ca 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 sinusoida omission of sodium ion or addition of the metab
inhibitors, 2,4-dinitrophenol and iodoacetate (1031).
cause liver slices contain both canalicular and sinuso
spaces, it is impossible with this technique to detern
whether th inhibitors, 2,4-dinitrophenol and iodoacetate (1031). Be-
cause liver slices contain both canalicular and sinusoidal tra
spaces, it is impossible with this technique to determine sul
whether this concentration gradient is cause liver slices contain both canalicular and sinusoidal the spaces, it is impossible with this technique to determine swhether this concentration gradient is due to accumulation of PAEB within the hepatocytes or within spaces, it is impossible with this technique to determine
whether this concentration gradient is due to accumula-
tion of PAEB within the hepatocytes or within the bile
canaliculi and sinusoidal spaces. PAEB is positively 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 pote tion 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
r canaliculi and sinusoidal spaces. PAEB is positively
charged regardless of pH and if one assumes a membrane per
potential of -35 mV (81), a slice/medium concentration thratio greater than 4 would be needed to demonstrat charged regardless of pH and if one assumes a membrane perpotential of -35 mV (81), a slice/medium concentration theratio greater than 4 would be needed to demonstrate muptake against an electrochemical gradient for a c potential of -35 mV (81), a slice/medium concentration the ratio greater than 4 would be needed to demonstrate muptake against an electrochemical gradient for a cation the rat, a liver/plasma ratio of unchanged PAEB of ratio greater than 4
uptake against an eleving in the set of the set of the rat, a liver/plasma rabeen reported (518).
Recently, isolated h take against an electrochemical gradient for a cation
no metabolism or intracellular binding occurred. In the
t, a liver/plasma ratio of unchanged PAEB of 7 has
en reported (518).
Recently, isolated hepatocytes have been u

if no metabolism or intracellular binding occurred. I
rat, a liver/plasma ratio of unchanged PAEB of 7
been reported (518).
Recently, isolated hepatocytes have been used to
onstrate that PAEB enters the liver by a carrierrat, a liver/plasma ratio of unchanged PAEB of 7 has
been reported (518).
Recently, isolated hepatocytes have been used to dem-
onstrate that PAEB enters the liver by a carrier-medi-
ated, saturable, and energy-dependent u 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

D WATKINS
from 30 to 400 μ M indicate a K_m of 54 μ M and V_{max} of
0.13 nmol/min/mg of protein. The process involves ac-D WATKINS
from 30 to 400 μ M indicate a K_m of 54 μ M and V_{max} of
0.13 nmol/min/mg of protein. The process involves ac-
tive transport because uptake against an electrochemical D WATKINS
from 30 to 400 μ M indicate a K_m of 54 μ M and V_{max}
0.13 nmol/min/mg of protein. The process involves a
tive transport because uptake against an electrochemic
gradient is evident even after correction fo from 30 to 400 μ M indicate a K_m of 54 μ M and V_n 0.13 nmol/min/mg of protein. The process involve
tive transport because uptake against an electrocher
gradient is evident even after correction for biotran
mation The matrix of the matrix of the matrix 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 in tive transport because uptake against an electrochemical
gradient is evident even after correction for biotransfor-
mation and intracellular binding. This system appears
to be distinct from those responsible for the accumu mation and intracellular binding. This system appears
to be distinct from those responsible for the accumula-
tion of neutral compounds such as ouabain or organic
anions like taurocholate. Whether more than one carrier
is 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 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). ions like taurocholate. Whether more than one carrier
responsible for hepatic uptake of organic cations is not
nown. Transport of numerous tertiary amines may
are a similar uptake system with PAEB (839).
5. Neutral Organic

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 sug-
gested that u known. Transport of numerous tertiary amines may
share a similar uptake system with PAEB (839).
5. Neutral Organic Compounds. Farah (323) first sug-
gested that uptake and excretion of ouabain might occur
by active transpo 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 5. Neutral Organic Compounds. Farah (323) first suggested that uptake and excretion of ouabain might occurs
by active transport because accumulation was inhibited
in rat liver slices by potassium cyanide. Ouabain uptake
is gested 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
a 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
 in rat liver slices by potassium cyanide. Ouabain upt
is a saturable, energy-dependent process that occagainst a concentration gradient and is not inhibited
organic anions or cations (696). Uptake is inhibited
other neutra 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, progester against a concentration gradient and is not inhibited by
organic anions or cations (696). Uptake is inhibited by
other neutral steroids such as corticosterone, progester-
one, testosterone, and dehydrocholate (695). These 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 b other neutral steroids such as corticosterone, progester-
one, testosterone, and dehydrocholate (695). These early
studies suggested that bile acids and ouabain might be
transported by the same carrier. However, developmen one, testosterone, and dehydrocholate (695). These e
studies suggested that bile acids and ouabain migh
transported by the same carrier. However, developme
studies (651) showed that taurocholate transport
near adult levels 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 is

in isolated hepatocytes (284, 1061). Uptake is saturable, 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,
wit near adult levels much earlier than that of ouabain.
Hepatic uptake for ouabain has been studied in det
in isolated hepatocytes (284, 1061). Uptake is saturab
with a K_m of 159 μ M and V_{max} of 1.43 nmol/min/mg
protei Hepatic uptake for ouabain has been studied in detail
in isolated hepatocytes (284, 1061). Uptake is saturable,
with a K_m of 159 μ M and V_{max} of 1.43 nmol/min/mg of
protein, and energy dependent as dinitrophenol, po in isolated hepatocytes (284, 1061). Uptake is saturable,
with a K_m of 159 μ M and V_{max} of 1.43 nmol/min/mg of
protein, and energy dependent as dinitrophenol, potas-
sium cyanide, and rotenone reduced ouabain transp with a K_m of 159 μ M 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 N protein, and energy dependent as dinitrophenol, potas-
sium cyanide, and rotenone reduced ouabain transport
into the hepatocytes. Ouabain uptake is independent of
Na⁺, which also indicates that its uptake is by a differe 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 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° 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 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 grad 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). 6. Ouabain is transported against a concentration gra-
dient 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
car dient and achieves a cell/medium ratio of about 10 (284). dient 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
h 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
transp Several steroidal compounds (six hormones and the cardiac glycosides) inhibit ouabain uptake into isolat hepatocytes, suggesting that they may share the satransport system (284). Recent work with hepatocy subpopulations in 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 centri-
lob hepatocytes, suggesting that the transport system (284). Recent subpopulations indicates ouaballobular-enriched population we periportal hepatocytes (1020). The uptake of galactose into ansport system (284). Recent work with hepatocyte byopulations indicates ouabain uptake into the centri-
bular-enriched population was greater than that into
riportal hepatocytes (1020).
The uptake of galactose into isolat

subpopulations indicates ouabain uptake into the centri-
lobular-enriched population was greater than that into
periportal hepatocytes (1020).
The uptake of galactose into isolated hepatocytes ap-
pears to be a carrier-med lobular-enriched population was greater than that
periportal hepatocytes (1020).
The uptake of galactose into isolated hepatocyte
pears to be a carrier-mediated diffusion process w
the rate of uptake greatly exceeds that o 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 biotransfor-
mation (80, 1020). This syst The uptake of galactose into
pears to be a carrier-mediated
the rate of uptake greatly excention (80, 1020). This system is
that which transports ouabain.
A biphasic system has been on ars to be a carrier-mediated diffusion process where
e rate of uptake greatly exceeds that of biotransfor-
ation (80, 1020). This system is probably different than
at which transports ouabain.
A biphasic system has been de

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 hepat mation (80, 1020). This system is probably different the that which transports ouabain.
A biphasic system has been demonstrated for cortiquation is belated hepatocyes (955) before the ster-
becomes bound to intracellular p 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 concen-

trations, uptake occu A biphasic system has been demonstrated for cortisol
uptake into isolated hepatocyes (955) before the steroid
becomes bound to intracellular proteins. At low concen-
trations, uptake occurs by two saturable processes with
 uptake into isolated hepatocyes (955) before the steroid
becomes bound to intracellular proteins. At low concen-
trations, uptake occurs by two saturable processes with
high and low affinities, respectively, which can be
b 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-dini

PHARMACOLOGICAL REVIEWS

BILE FORMATION, HEPATIC UPTAKE, AND BILIARY EXCRETION
tions, simple diffusion becomes the major route of cor- ber of binding sites after cycl
tisol uptake into hepatocytes. Cortisone and corticoster- receptors may be the b BILE FORMATION, HEPATI
tions, simple diffusion becomes the major route of
tisol uptake into hepatocytes. Cortisone and corticos
one are competitive inhibitors while dexamethasone BILE FORMATION, HEPATIC UPT
tions, simple diffusion becomes the major route of cor-
tisol uptake into hepatocytes. Cortisone and corticoster-
one are competitive inhibitors while dexamethasone, es-
trone, and testosterone tions, simple diffusion becomes the major route of cortisol uptake into hepatocytes. Cortisone and corticoster-
one are competitive inhibitors while dexamethasone, es-
trone, and testosterone are non-competitive inhibitors tisol uptake into hepatocytes. Cortisone and corticoster-
one are competitive inhibitors while dexamethasone, es-
trone, and testosterone are non-competitive inhibitors of
cortisol uptake. Additional studies indicate estro trone, and testosterone are non-competitive inhibitors of
cortisol uptake. Additional studies indicate estrone, es-
tradiol, and testosterone also enter hepatocytes by dif-
fusion and by carrier-mediated transport (954). S cortisol uptake. Additional studies indicate estrone, esfusion and by carrier-mediated transport (954) . Similar
findings have been observed for the uptake of tri-iodothy-
ronine by isolated (290) and cultured $(685, 686)$ hepato-
cytes.
6. *Metals*. A biphasic mechanism is cytes. is ion and by carrier-mediated transport (954). Similar inclings have been observed for the uptake of tri-iodothy-

mine by isolated (290) and cultured (685, 686) hepato-

the s.

6. Metals. A biphasic mechanism is involve

findings have been observed for the uptake of tri-iodothy-

ronine by isolated (290) and cultured (685, 686) hepato-

the surface of zinc and cadmium. Studies on cadmium

hepatic uptake of zinc and cadmium. Studies on cad ronine 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, cytes.

6. Metals. A biphasic mechanism is involved in the shepatic uptake of zinc and cadmium. Studies on cadmium

transport in isolated perfused rat liver (361, 362, 606)

and suspensions of isolated hepatocytes (1121) 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) indicat 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-med 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
 a simple diffusion phase as well as a carrier-mediated
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. Pre-
t phase that can be inhibited by zinc. Neither phase is
affected by administration of metabolic inhibitors. Pre-
treatment of rats with cadmium chloride, which increases
hepatic metallothionein content (288, 1073, 1241, 1242 phase that can be inhibited by zinc. Neither phase is affected by administration of metabolic inhibitors. Pre-
treatment of rats with cadmium chloride, which increases
hepatic metallothionein content (288, 1073, 1241, 124 affected by administration of metabolic inhibitors. Precentement of rats with cadmium chloride, which increase
hepatic metallothionein content (288, 1073, 1241, 124
1272), increases the rate of the diffusion phase of uptal treatment of rats with cadmium chloride, which increase
hepatic metallothionein content (288, 1073, 1241, 12
1272), increases the rate of the diffusion phase of upts
(1121). This diffusion phase may be related to the int
c hepatic metallothionein content (288, 1073, 124
1272), increases the rate of the diffusion phase of
(1121). This diffusion phase may be related to the
cellular sequestering of cadmium by metalloth
Cadmium complexes with di 1272), increases the rate of the diffusion phase of update

(1121). This diffusion phase may be related to the intra-

cellular sequestering of cadmium by metallothionein.

Cadmium complexes with dithiols $(2,3$ -dimercapt (1121). This diffusion phase may be related to the intra
cellular sequestering of cadmium by metallothionein
Cadmium complexes with dithiols $(2,3$ -dimercaptopro-
panol, dithiothreitol) are rapidly removed from the
plasma cellular sequestering of cadmium by metallothionein
Cadmium complexes with dithiols (2,3-dimercaptopro
panol, dithiothreitol) are rapidly removed from th
plasma by Kupffer cells (1096) while either free or non
thiol comple Cadmium conditationally K

plasma by K

thiol comple:

cells (154).

A similar l mol, dithiothreitol) are rapidly removed from the first phase aby Kupffer cells (1096) while either free or noise iol complexes of cadmium are taken up by parenchym
lls (154).
A similar biphasic response with the first pha

thiol complexes of cadmium are taken up by parenchymal
cells (154) .
A similar biphasic response with the first phase show-
ing characteristics of carrier-mediated transport has m
been observed for the uptake of zinc int cells (154).

A similar biphasic response with the first phase show-

lating characteristics of carrier-mediated transport has

ma

been observed for the uptake of zinc into 3T3 mouse a m

lymphocytes (1049), isolated rat A similar biphasic response with the first phase show-
ing characteristics of carrier-mediated transport has
been observed for the uptake of zinc into 3T3 mouse
any
hymphocytes (1049), isolated rat hepatocytes (1121), and 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 en observed for the uptake of zinc into 3T3 mouse a m
mphocytes (1049), isolated rat hepatocytes (1121), and wor
imary cultures of rat liver cells for zinc (320, 321) and need
mium (322).
Ferrous iron is taken up by hepato

lymphocytes (1049), isolated rat hepatocytes (1121), primary cultures of rat liver cells for zinc (320, 321) cadmium (322).
cadmium (322).
Ferrous iron is taken up by hepatocyte suspensions
simple diffusion while that of f 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 upta 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 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 h 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 ironmediated. Transferrin-bound iron uptake is biphareceptor-mediated at low concentrations and by diffus
at higher levels (435). Uptake of ferric iron from iron
transferrin depends on temperature and the transfer
concentratio 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
goncentration and is inhibited by exposure of hepatoat higher levels (435). Uptake of ferric iron fit
transferrin depends on temperature and the transferrin depends on temperature and the transferred
cytes to proteases (1291). These data support to
a surface receptor-mediat *Concentration and is inhibited by exposure of hepatocytes to proteases (1291). These data support the role of a surface receptor-mediated uptake component.

<i>D. Macromolecules in Hepatic Uptake*
 1. Membrane Receptors.

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 D. Macromolecules in Hepatic Uptake
1. Membrane Receptors. a. BILE ACIDS. Specific
acid binding sites on liver surface membranes have b
postulated to represent the initial step in bile acid tra
location across the hepatocy 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 trans-
location across the hepatocyte membrane (11). Pretre acid binding sites on liver surface membranes have been
postulated to represent the initial step in bile acid trans-
location across the hepatocyte membrane (11). Pretreat-
ment of rats with cycloheximide to block hepatic postulated to represent the initial step in bile acid trans-
location across the hepatocyte membrane (11). Pretreat-
ment of rats with cycloheximide to block hepatic protein
synthesis reduced bile acid transport capacity t location across the hepatocyte membrane (11). Pretreat ment 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, ment of rats with cycloheximide to block hepatic protein
synthesis reduced bile acid transport capacity to 38% of
ment control. Values of liver function tests, bile flow, and
diffusiological profiles were all normal. The synthesis reduced bile acid transport capacity to 38% of m
control. Values of liver function tests, bile flow, and d
histological profiles were all normal. The maximum num-
ber of $[^{14}C]$ cholic acid binding sites was re control. Values of liver function tests, bile flow
histological profiles were all normal. The maximum
ber of $[^{14}C]$ cholic acid binding sites was reduced 7!
hours after cycloheximide, while no effect was obs
on the acti ber of 1^{4} C]cholic acid binding sites was reduced 75% 2 hours after cycloheximide, while no effect was observe on the activities of the marker enzymes, Na^{+} -K⁺-ATF ase, Mg^{++} -ATF ase, or 5'-nucleotidase. The asso

kke, AND BILIARY EXCRETION 23
ber of binding sites after cycloheximide suggests these
receptors may be the bile acid carriers (398). RE, AND BILIARY EXCRETION
ber of binding sites after cycloheximide suggeneceptors may be the bile acid carriers (398).
The liver responds to an increased bile aci

E, AND BILIARY EXCRETION 23

The liver responds to an increased bile acid load by

The liver responds to an increased bile acid load by

The liver responds to an increased bile acid load by

creasing the bile acid excretor ber 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 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 num 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 increasing the bile acid excretory maximum (14, 109, 1235). This substrate-induced effect produces an increased in the number of bile acid receptors which may occur vincreased protein synthesis, decreased receptor degradat 1235). This substrate-induced effect produces an increase
in the number of bile acid receptors which may occur via
increased protein synthesis, decreased receptor degra-
dation, or a shifting from a possible intracellular 1235). This substrate-induced effect produces an increase
in the number of bile acid receptors which may occur vii
increased protein synthesis, decreased receptor degra
dation, or a shifting from a possible intracellular p in the number of bile acid receptors which may occur via
increased protein synthesis, decreased receptor degra-
dation, or a shifting from a possible intracellular pool to
the surface membrane (1092). Whatever the mechanis morecased procem symmetric, accreased receptor alged
dation, 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 the surface membrane (109)
the number of putative bile
adapt to the taurocholate
needed to characterize this
chemically and functionally
b. ORGANIC ANIONS. AI e number of putative bile acid carriers can apparently
lapt to the taurocholate pool size. Further work is
eded to characterize this bile acid receptor both bio-
emically and functionally.
b. ORGANIC ANIONS. An integral pr

hepatocyte plasma membrane has been isolated that
hepatocyte plasma membrane has been isolated that
exhibits a high affinity for BSP (1183). This protein was needed to characterize this bile acid receptor both bio-
chemically and functionally.
b. ORGANIC ANIONS. An integral protein from the
hepatocyte plasma membrane has been isolated that
exhibits a high affinity for BSP (1183 chemically 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 of channel antotic. 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 li 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
ex 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 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
p 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
pr extraction and chromatographed on Sephadex G-100 a
then AG-1X8 resin. Based on BSP binding, this isolati
procedure gave an approximate 40% yield of BSP bindi
protein that can bind 100 nmol of BSP per milligram
protein. Thi 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 a protein that can bind 100 nmol of BSP per milligram of
protein. This receptor is a single protein with an appar-
ent molecular weight of 170,000 and has a dissociation
constant for BSP around 4μ M.
An organic anion bind otein that can bind 100 nmol of BSP per milligram of
otein. This receptor is a single protein with an appar-
t molecular weight of 170,000 and has a dissociation
nstant for BSP around 4 μ M.
An organic anion binding pro

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 show-
lated from rat liver plasma membrane by a protein. This receptor is a single protein with an apparent molecular weight of 170,000 and has a dissociatio constant for BSP around 4 μ M.
An organic anion binding protein has also been isolated from rat liver plasma ent molecular weight of 170,000 and has a dissociation
constant for BSP around 4μ M.
An organic anion binding protein has also been iso-
lated from rat liver plasma membrane by affinity chro-
matography on bilirubin and constant for BSP around 4μ M.
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 approximat An organic anion binding protein has also been iso-
lated from rat liver plasma membrane by affinity chro-
matography on bilirubin and BSP-agarose (964). It has
a molecular weight of approximately 60,000. More recent
work lated 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 nee matography 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
capa 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 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 s 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 capacities of 3.5×10^{-11} , 1.6×10^{-7} , and 5.4×10^{-7} mol
mg of protein (966). BSP-glutathione binding sites ha
maximal capacities of 5×10^{-11} and 2×10^{-7} mol/mg of
protein. BSP-glutathione, indocyanine g 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 bili-
rubin, but not taurocholate, compete with BSP for protein. BSP-glutathione, indocyanine green, and bili-
rubin, but not taurocholate, compete with BSP for bind-
ing. Demonstration of a saturable binding site with
greater affinity for BSP than albumin or ligandin sugrubin, but not taurocholate, compete with BSP for binding. Demonstration of a saturable binding site with ions. hepatocyte plasma membrane has been isolated that
exhibits a high affinity for BSP (1183). This protein was
exparated from an acetone powder of a crude preparation
of rat liver plasma membrane that was subjected to salt
e

cytes to proteases (1291). These data support the role of for hepatic uptake and biliary excretion of organic an-
ions.
D. Macromolecules in Hepatic Uptake Further studies (1280) indicate isolation of a 5500
1. Membran and saturable binding $(6.3 \text{ nmol/mg of protein})$ for BSP. for hepatic uptake and biliary excretion of organic an-
ions.
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) fo ions.
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 ligan Further studies (1280) indicate isolation of a is
dalton protein which has high affinity $(K_a = 0.27 \mu)$
and saturable binding (6.3 nmol/mg of protein) for E
This protein is immunologically distinct from ligar
and rat album allow protein which has high all intrity $(K_a - 0.27 \mu M)$
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

histological profiles were all normal. The maximum num-
ber of $[^{14}C]$ cholic acid binding sites was reduced 75% 24 known. Also, it is not known whether these BSP binding
hours after cycloheximide, while no effect was ob This protein is immunologically distinct from ligand
and rat albumin and binds bilirubin $(K_d = 20 \,\mu\text{M})$.
Thus, three groups have isolated proteins from plass
membranes of liver that bind BSP. Whether the mark
difference 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 differ-
ences in 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 differ-
ences in polymer formation or to distinct proteins is not
kn membranes of liver that bind BSP. Whether the marked
differences in molecular weights may be due to differ-
ences in polymer formation or to distinct proteins is not
known. Also, it is not known whether these BSP binding
p 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
 ences 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 fo 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
re

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

KLAASSEN AND
wn sheep and fetal or neonatal animals) may elucidate
e relationship of this receptor to hepatic transport.
c. DESIALYLATED GLYCOPROTEINS. Rapid removal of
rculating desialylated glycoproteins from blood of o down sheep and fetal or neonatal animals) may elucidate
the relationship of this receptor to hepatic transport.
c. DESIALYLATED GLYCOPROTEINS. Rapid removal of
picrolating desialylated glycoproteins from blood of or
mammal down sheep and fetal or neonatal animals) may elucidate brather elationship of this receptor to hepatic transport. bett c. DESIALYLATED GLYCOPROTEINS. Rapid removal of particirculating desialylated glycoproteins from blood a carbohydrate recognition system present only on hep-
circulating desialylated glycoproteins from blood of
mammals occurs exclusively by liver and is mediated by
a carbohydrate recognition system present only on hep
atocy circulating desialylated glycoproteins from blood of of
mammals occurs exclusively by liver and is mediated by
a carbohydrate recognition system present only on hep-
tratocytes (845, 1047). This cell surface receptor recog mammals occurs exclusively by liver and is mediated by
a carbohydrate recognition system present only on hep-
atocytes (845, 1047). This cell surface receptor recog-
nizes, binds, and internalizes molecules having exposed
 a carbohydrate recognition system present only on hep-
atocytes (845, 1047). This cell surface receptor recog-
nizes, binds, and internalizes molecules having exposed
aresidues of galactose, N-acetylgalactosamine, and gluatocytes (845, 1047). This cell surface receptor recognizes, binds, and internalizes molecules having exposed
residues of galactose, N-acetylgalactosamine, and glu-
cose. After internalization via coated pits and coated
ve nizes, binds, and internalizes molecules having exposed
residues of galactose, N-acetylgalactosamine, and glu-
cose. After internalization via coated pits and coated
vesicles, desialylated glycoproteins subsequently appear residues of galactose, N-acetylgalactosamine, and glucose. After internalization via coated pits and coated c
vesicles, desialylated glycoproteins subsequently appear p
in a complex network of tubules and uncoated vesicles cose. 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 (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 × 10⁴ receptors/ 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 \times 10⁴ recepto before reaching the lysosomes where they are degraded T
(279, 513, 1226, 1227). Studies in isolated hepatocytes poidicate only 5% of the receptors (6.7 \times 10⁴ receptors/ th
cell) are present on the external surface of (279, 513, 1226, 1227). Studies in isolated hepatocytes poundicate only 5% of the receptors (6.7 \times 10⁴ receptors/ the cell) are present on the external surface of the sinusoidal manembrane and the rest are in the cyt indicate only 5% of the receptors $(6.7 \times 10^4$ receptors/ th
cell) are present on the external surface of the sinusoidal ma
membrane and the rest are in the cytoplasm. Ligand the
binding to the receptor is time-dependent receptor is apparently stable under conditions where the biggand is being destroyed and here conditions where the biggand is being destroyed and hence undergoes recycling no linear the biggand is being destroyed and hence membrane and the rest are in the cytoplasm. Ligand the binding to the receptor is time-dependent, saturable, and the dissociable $(K_d = 3.4 \times 10^{-8} M)$ (1124). Furthermore, the 5 receptor is apparently stable under condition binding to the receptor is time-dependent, saturable, dissociable $(K_d = 3.4 \times 10^{-8} M)$ (1124). Furthermore, receptor is apparently stable under conditions where ligand is being destroyed and hence undergoes recycles are lo 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 intra receptor is apparently stable under conditions where the ligand is being destroyed and hence undergoes recycling such that most receptor molecules are located intracel-lularly (1160) . In spite of the 50% reduction of re ligand is being destroyed and hence undergoes recycling
such that most receptor molecules are located intracel-
lularly (1160). In spite of the 50% reduction of receptor
protein by inclusion of cycloheximide in the medium, such that most receptor molecules are located intracel-
lularly (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
t lularly (1160). In spite of the 50% reduction of recepto
protein by inclusion of cycloheximide in the medium
metabolism of asialo-orosomucoid was 34 times greate
than the amount that could be bound to the recepto
(1124), w 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 recy-
cling. Molecular weights for the asialoglycoprotein bind-
in than the amount that could be bound to the receptor (1124) , which supports the hypothesis of receptor-recy-(1124), which suppose the hypothesis of receptor recy-
cling. Molecular weights for the asialogly coprotein bind-
ing receptor are 104,000 and 109,000 for rat and rabbit,
respectively (1125). Infusion of receptor-specific that the receptor is essential for clearance of desialo-oro-
somucoid but not that of bilirubin, thereby suggesting
that the receptor is essential for clearance of desialylated
glycoproteins (1139).
Approximately 70% to 80 My substantially reduces hepatic uptake of asialo-oro-
mucoid but not that of bilirubin, thereby suggesting
at the receptor is essential for clearance of desialylated
ycoproteins (1139).
Approximately 70% to 80% of an intr

somucoid 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 ad-
ministered dose of mannosaminated r that the receptor is essential for clearance of desialylated
glycoproteins (1139).
Approximately 70% to 80% of an intravenously ad-
ministered dose of mannosaminated ribonuclease A di-
mer and serum albumin is taken up by glycoproteins (1139). I
Approximately 70% to 80% of an intravenously ad-
ministered dose of mannosaminated ribonuclease A di-
mer and serum albumin is taken up by the endothelial f
and Kupffer cells of the liver (1270). S 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-gly ministered dose of mannosaminated ribonuclease A
mer and serum albumin is taken up by the endothel
and Kupffer cells of the liver (1270). Since hepatic upta
of non-glycosaminated derivatives was $\leq 5\%$, these p
teins a mer and serum albumin is taken up by the endothelial
and Kupffer cells of the liver (1270) . Since hepatic uptake
of non-glycosaminated derivatives was $\leq 5\%$, these pro-
teins are thought to enter hepatocytes via the teins are thought to enter hepatocytes via the desialy-

ated saturable process with high affinity for the lipoprolated glycoprotein receptor-mediated carrier.
d. LIPOPROTEINS. Hepatic uptake of E apoprotein from
high density lipoproteins by rat liver is a receptor-medi-
ated saturable process with high affinity for the lipopro-
tein d. LIPOPROTEINS. Hepatic uptake of E apoprotein from one high density lipoproteins by rat liver is a receptor-medi-
ated saturable process with high affinity for the lipopro-
tein (1083). Results suggest that the mechanism high density lipoproteins by rat liver is a receptor-medi-
ated saturable process with high affinity for the lipopro-
tein (1083). Results suggest that the mechanism of up-
take is identical for that of chylomicron remnant ated saturable process with high affinity for the lipopro-
tein (1083). Results suggest that the mechanism of up-
take is identical for that of chylomicron remnants, and
that E apoprotein is the receptor recognition site f tein (1083). Results suggest that the mechanism of up-
take 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,
 that E apoprotein is the receptor recognition site for h .
chylomicron uptake into liver (164, 165, 173). However, volve
non-parenchymal as well as parenchymal cells are in-
volved in the uptake of cholesterol ester-labe 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 importanc of 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

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 t of non-phagocytosing parenchymal cells in the clearanch of endogenous compounds.

e. ENDOTOXINS. Receptors for the lipopolysaccharic endotoxin have been detected on the plasma membranch of isolated rabbit hepatocytes (953)

b WATKINS
brane increases directly with endotoxin concentration
between 0.01 to 1.0 mg/ml. Results demonstrate that D WATKINS
brane increases directly with endotoxin concentration
between 0.01 to 1.0 mg/ml. Results demonstrate that
parenchymal cells are also involved in hepatic clearance D WATKINS
brane 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. brane increa
between 0.01
parenchymal
of endotoxin
f. IMMUNO fut tween 0.01 to 1.0 mg/ml. Results demonstrate the
renchymal cells are also involved in hepatic clearance
endotoxin.
f. IMMUNOGLOBULINS AND IMMUNE COMPLEXES. In
avenously administered immunological aggregates are

parenchymal cells are also involved in hepatic clearance
of endotoxin.
f. IMMUNOGLOBULINS AND IMMUNE COMPLEXES. In-
travenously administered immunological aggregates are
taken up by and sequestered in hepatocytes of rabbit parenchymal cells are also involved in hepatic clearance
of endotoxin.
f. IMMUNOGLOBULINS AND IMMUNE COMPLEXES. In-
travenously administered immunological aggregates are
taken up by and sequestered in hepatocytes of rabbit of endotoxin.

f. IMMUNOGLOBULINS AND IMMUNE COMPLEXES. In-

travenously administered immunological aggregates are

taken up by and sequestered in hepatocytes of rabbits

and rhesus monkeys (772). Receptors for the Fc port f. IMMUNOGLOBULINS AND IMMUNE COMPLEXES. In
travenously administered immunological aggregates are
taken up by and sequestered in hepatocytes of rabbit
and rhesus monkeys (772). Receptors for the Fc portion
of immunoglobul travenously 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
compone 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
plasm 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
compl of immunoglobulin G (IgG) and the third complemen
component (C3) have been localized on the hepatocyt
plasma membrane (368, 505). Small amounts of immun
complexes are taken up by non-parenchymal cells (506)
The mechanism f 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 com-
pou 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 com-
pounds such as human IgG by mouse hepatocytes is
thought to in complexes are taken up by non-parenchymal cells (506).
The mechanism for the in vivo uptake of foreign com-
pounds such as human IgG by mouse hepatocytes is
thought to involve binding to a receptor followed by
macropinocyt 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 clearanc 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,
5 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,
5 macropinocytosis (44). Extensive work has characteriz
the clearance of IgA and IgA antibodies from blood
the liver and subsequent active transport into bile (1
547, 562, 671, 725, 884). The uptake process appears
be initia the clearance of IgA and IgA antibodies from blood t
the liver and subsequent active transport into bile (10
547, 562, 671, 725, 884). The uptake process appears t
be initiated by binding to a receptor, secretory compo
nen 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 compo-
nent, which is found on the sinusoidal surface of hep 547, 562, 671, 725, 884). The uptake process appears to
be initiated by binding to a receptor, secretory compo-
nent, which is found on the sinusoidal surface of hepa-
tocytes (347, 883). Receptor-mediated endocytosis is g nent, 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 recep tocytes (347, 883). Receptor-mediated endocytosis is generally associated with coated pits and coated vesicles
(318). However, elucidation of the structure of the recep-
tor and the mechanism initiating the formation of ve tor and the mechanism initiating the formation of vesierally associated with coated pits and coated vesite (318). However, elucidation of the structure of the rector and the mechanism initiating the formation of vector are needed before a complete understanding of uptake of 18). However, elucidation of the structure of the recep-
r and the mechanism initiating the formation of vesi-
es are needed before a complete understanding of the
take of immunological complexes can be achieved.
g. INSUL

and Kupffer cells of the liver (1270). Since hepatic uptake both receptor and insulin are internalized (1172). Light
of non-glycosaminated derivatives was $\leq 5\%$, these pro-
teins are thought to enter hepatocytes via t tor 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 cles are needed before a complete understanding of the uptake of immunological complexes can be achieved.
g. INSULIN. The initial interaction of 125 [-insulin with binding sites on the hepatocyte plasmalemma was demonstr uptake of immunological complexes can be achieved.
g. INSULIN. The initial interaction of ¹²⁵I-insulin with
binding sites on the hepatocyte plasmalemma was dem-
onstrated by electron microscope radioautography (89).
Resu 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 no onstrated by electron microscope radioautography (89). Results showed that binding distributed evenly over the sinusoidal and lateral surfaces of the hepatocyte and was sinusoidal and lateral surfaces of the hepatocyte and was
notably absent from the canalicular membrane (90).
Interaction of hormone with receptor activates pinocy-
tosis and the formed vesicle is transported through the
cy notably absent from the canalicular membrane (90).
Interaction of hormone with receptor activates pinocy-
tosis and the formed vesicle is transported through the
cytoplasm to the Golgi apparatus. Biochemical evidence
from tosis and the formed vesicle is transported through the cytoplasm to the Golgi apparatus. Biochemical evidence from studies with isolated hepatocytes indicates that cytoplasm to the Golgi apparatus. Biochemical evidence eyophasm to the congr apparatus. Blochemical evidence
from studies with isolated hepatocytes indicates that
both receptor and insulin are internalized (1172). Light
and electron microscopic observations suggest that the
pi both receptor and insulin are internalized (1172). Light
and electron microscopic observations suggest that the
pinocytotic process is probably activated by high concen-
trations of hormone as grains visually appeared clos 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-specif 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-specif trations 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 recept one pole of the membra
(89, 90). Photoaffini
antibodies have been
(548, 1290); however,
completely determined
h. OTHER CHEMICA 9, 90). Photoaffinity-labeling and receptor-specific
tibodies have been used to characterize this receptor
48, 1290); however, its biological importance is not
mpletely determined.
h. OTHER CHEMICALS. Additional receptors

antibodies have been used to characterize this re

(548, 1290); however, its biological importance

completely determined.

h. OTHER CHEMICALS. Additional receptors a

volved in uptake of fatty acids (976), hemoglobii

tog (548, 1290); however, its biological importance is not completely determined.

h. OTHER CHEMICALS. Additional receptors are involved in uptake of fatty acids (976), hemoglobin-hap-toglobin (607), transcobalamin (848), and completely determined.

h. OTHER CHEMICALS. Additional receptors are in-

volved in uptake of fatty acids (976), hemoglobin-hap-

toglobin (607), transcobalamin (848), and several hor-

mones such as growth hormone (360), h. OTHER CHEMICALS. Additional receptors are in-
volved in uptake of fatty acids (976), hemoglobin-hap-
toglobin (607), transcobalamin (848), and several hor-
mones such as growth hormone (360), prolactin (121),
estradiol volved in uptake of fatty acids (976), hemoglobin-ha
toglobin (607), transcobalamin (848), and several h
mones such as growth hormone (360), prolactin (12
estradiol (922), etc. A recent review discusses propert
of these re toglobin (607), transcobalamin (848), and several ho
mones such as growth hormone (360), prolactin (121
estradiol (922), etc. A recent review discusses propertio
of these receptors, transmembrane movement of endo
enous and mones such as growth
estradiol (922), etc. A re
of these receptors, trans
enous and exogenous con
brane biogenesis (318).
2. Intracellular Prote 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

BILE FORMATION, HEPATIC UPTAKE, AND BILIARY EXCRETION ²⁵ BILE FORMATION, HEPATIC UPTA
cytosol on the basis of their ability to bind organic anions
(348, 728, 981). Y protein, quantitatively the more im-BILE FORMATION, HEPATIC UP

eytosol on the basis of their ability to bind organic anions

(348, 728, 981). Y protein, quantitatively the more im-

portant protein, has been purified to homogeneity and BILE FORMATION, HEPATIC UPTAKI
cytosol on the basis of their ability to bind organic anions
(348, 728, 981). Y protein, quantitatively the more im-
portant protein, has been purified to homogeneity and
sume found to bind v cytosol on the basis of their ability to bind organic anions bloc (348, 728, 981). Y protein, quantitatively the more im-
lula portant protein, has been purified to homogeneity and sugg
found to bind various drugs, hormone (348, 728, 981). Y protein, quantitatively the more im-
portant protein, has been purified to homogeneity and
found to bind various drugs, hormones, and metabolites
(540). This protein was termed ligandin and proposed to
b lular binding function (586, 1279). Although no evidence lular binding function (1586)
himited to performing an intracel-
hilar binding function (586, 1279). Although no evidence
suggests these proteins are responsible for recognition sum these proteins are responsible for recognitional photod to bile is mainly limited to performing an intracel-
hular binding function (586, 1279). Although no evidence
suggests these proteins are responsible for recognit blood to bile is mainly limited to performing an intrace
lular binding function (586, 1279). Although no evidence
suggests these proteins are responsible for recognitio
and uptake of organic anions from vascular space, bin

(040). This protein was termed inguitant 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
l

liver of newborn guinea pigs (728) and monkeys (7:
was suggested to account for the observed neonatal u
conjugated hyperbilirubinemia. Normalization of hepa
organic anion transport coincided with growth and t
appearance of 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 demonstrate conjugated hyperbilirubinemia. Normalization of hepat
organic anion transport coincided with growth and the
appearance of ligandin. 2) A phylogenetic study demos
strated that the elasmobranch bony fish and the gil
breathin

appearance of ligandin. 2) A phylogenetic study dem
strated that the elasmobranch bony fish and the g
breathing mudpuppy have no detectable levels of lig
din, have ony trace amounts of Z protein, and li
selective BSP uptak strated that the elasmobranch bony fish and the gill-
breathing mudpuppy have no detectable levels of ligan-
din, have ony trace amounts of Z protein, and lack
selective BSP uptake. All tested lung-breathing amphib-
ians,

din, have ony trace amounts of Z protein, and la
selective BSP uptake. All tested lung-breathing amph
ians, reptiles, birds, and mammals have apprecia
levels of Y and Z proteins and hepatic organic an
uptake (731). In addi

ians, reptiles, birds, and mammals have appreciablevels of Y and Z proteins and hepatic organic anic uptake (731). In addition, there is an apparent correlition between hepatic BSP uptake and content of solub binding prote

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 af tion between hepatic BSP uptake and content of soluble
binding proteins. Furthermore, ligandin, which is unde-
tectable in gill-breathing tadpoles, becomes detectable
after metamorphosis to lung-breathing adult frogs (731) 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 metamorphosis to lung-breathing adult frogs (731).
3) The concentration of ligandin in rat liver increases
after administration of phenobarbital, *trans*-stilbene ox-
ide, or butylated hydroxyanisole and is associat

after administration of phenobarbital, *trans*-stilbene oxide, or butylated hydroxyanisole and is associated with a concurrent enhancement of anion uptake (348, 429, 981). Pregnenolone-16 α -carbonitrile induces ligandin

concurrent enhancement of anion uptake $(348, 429, 981)$.
Pregnenolone-16 α -carbonitrile induces ligandin and
doubles BSP and bilirubin binding (758). However, con-
flicting data indicate binding to ligandin is not the regnemome-roa-canomicine mattes inguitant and
doubles BSP and bilirubin binding (758). However, con-
flicting data indicate binding to ligandin is not the sole
determinant of hepatic organic ion uptake. 1) Mutant
Southdown

determinant of hepatic organic ion uptake. 1) Mutant

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 cor

zyme 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
 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,
up

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
re 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

reduced in hypophysectomized and thyroidectomize
rats although ligandin is increased (981). 7) In vitr
ligandin has a lower affinity for BSP and bilirubin the
does albumin, yet these compounds are readily remove
from album

ligandin has a lower affinity for BSP and bilirubin t
does albumin, yet these compounds are readily remo
from albumin during hepatic uptake (364, 583, 1281)
More recent experiments demonstrate a decreas
bilirubin or DBSP e

found to bind various drugs, hormones, and metabolites and uptake of organic anions from vascular space, bind-

(540). This protein was termed ligandin and proposed to ing to these proteins can reduce anion efflux into pla following indirect data. 1) A deficiency of ligandin in during gel filtration became conjugated to glutathione
liver of newborn guinea pigs (728) and monkeys (729) (GSH) (589). Subsequently, ligandin was demonstrated
was s conjugated hyperbilirubinemia. Normalization of hepatic GS
was suggested to account for the observed neonatal un-
conjugated hyperbilirubinemia. Normalization of hepatic GS
organic anion transport coincided with growth and organic anion transport coincided with growth and the it happearance of ligandin. 2) A phylogenetic study demon-
strated that the elasmobranch bony fish and the gill-
anion-
breathing mudpuppy have no detectable levels of breathing mudpuppy have no detectable levels of ligan-
din, have ony trace amounts of Z protein, and lack
selective BSP uptake. All tested lung-breathing amphib-
ians, reptiles, birds, and mammals have appreciable do
level selective BSP uptake. All tested lung-breathing amphib- on ligandin. In fact, many organic anions including in-
ians, reptiles, birds, and mammals have appreciable docyanine green and bilirubin bind non-covalently to
level levels of Y and Z proteins and hepatic organic anion
uptake (731). In addition, there is an apparent correla-
tion between hepatic BSP uptake and content of soluble
binding proteins. Furthermore, ligandin, which is unde-
t blood to bile is mainly limited to performing an intracel-
lular binding function (586, 1279). Although no evidence
suggests these proteins are responsible for recognition
and uptake of organic anions from vascular space, lar binding function (586, 1279). Although no evidence
ggests these proteins are responsible for recognition
d uptake of organic anions from vascular space, bind-
g to these proteins can reduce anion efflux into plasma.
Ho suggests these proteins are responsible for recognition
and uptake of organic anions from vascular space, bind-
ing to these proteins can reduce anion efflux into plasma.
However, an additional function of ligandin was dis and uptake of organic anions from vascular space, bind-
ing to these proteins can reduce anion efflux into plasma.
However, an additional function of ligandin was dis-
covered in 1973 when the BSP that bound to ligandin
du ing to these proteins can reduce anion efflux into plasma.
However, an additional function of ligandin was dis-
covered in 1973 when the BSP that bound to ligandin
during gel filtration became conjugated to glutathione
(GS 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 ident covered 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
GS 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). Rece (GSH) (589). Subsequently, ligandin was demonstrat
to be identical to GSH S-transferase B, one of six distin
GSH transferases in rat liver cytosol (450, 451). Recen
it has been demonstrated that BSP binding to ligano
was n to be identical to GSH S-transferase B, one of six distint GSH transferases in rat liver cytosol (450, 451). Recentit has been demonstrated that BSP binding to ligand was not affected by the presence of bilirubin or indoca 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 indocy-
anine green; however, conjugation of BSP was signifi it has been demonstrated that BSP binding to ligandin
was not affected by the presence of bilirubin or indocy-
anine green; however, conjugation of BSP was signifi-
cantly reduced by the latter anion (230). Results suggest was not affected by the presence of bilirubin or indocy-
anine green; however, conjugation of BSP was signifi-
cantly reduced by the latter anion (230). Results suggest
the presence of catalytic and non-catalytic binding s anine 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 cantly 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 in-
docyanine green and bilirubin bind non-covalently the presence of catalytic
on ligandin. In fact, ma
docyanine green and b
GSH transferases but a
601, 739, 1093).
Butylated hydroxyani ligandin. In fact, many organic anions including in-
cyanine green and bilirubin bind non-covalently to
SH transferases but are not conjugated (103, 584, 585,
1, 739, 1093).
Butylated hydroxyanisole and *trans*-stilbene ox

tectable in gill-breathing tadpoles, becomes detectable ten
after metamorphosis to lung-breathing adult frogs (731). The
3) The concentration of ligandin in rat liver increases of l
after administration of phenobarbital, 3) The concentration of ligandin in rat liver increases of latter administration of phenobarbital, *trans*-stilbene oxide, or butylated hydroxyanisole and is associated with a concurrent enhancement of anion uptake $(348,$ ide, or butylated hydroxyanisole and is associated with a
concurrent enhancement of anion uptake $(348, 429, 981)$. ex-
Pregnenolone-16 α -carbonitrile induces ligandin and tion
doubles BSP and bilirubin binding (758) . docyanine 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 l GSH transferases but are not conjugated (103, 584, 585, 601, 739, 1093).

Butylated hydroxyanisole and *trans*-stilbene oxide in-

duce GSH S-transferase, increase hepatic ligandin con-

tent, and enhance the biliary excre 601, 739, 1093).
Butylated hydroxyanisole and *trans*-stilbene oxide in-
duce GSH S-transferase, increase hepatic ligandin con-
tent, and enhance the biliary excretion of BSP (429).
These treatments did not enhance the bil Butylated hydroxyanisole and *trans*-stilbene oxide in-
duce GSH S-transferase, increase hepatic ligandin con-
tent, and enhance the biliary excretion of BSP (429).
These treatments did not enhance the biliary excretion
of tent, 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 impor-
tan tent, 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 impor-
tan These treatments did not enhance the biliary excret of DBSP, a phthalein dye that binds to ligandin bunot conjugated with GSH. Thus, ligandin is more imptant as an enzyme than as a binding protein for excretion of phthalei of DBSP, a phthalein dye that binds to ligandin but is
not conjugated with GSH. Thus, ligandin is more impor-
tant as an enzyme than as a binding protein for the
excretion of phthalein dyes. Also, the hepatic accumula-
tio not conjugated with GSH. Thus, ligatent as an enzyme than as a bind
excretion of phthalein dyes. Also, the
tion of biliary contrast agents does
binding to cytosolic proteins (738).
b. METALLOTHIONEIN (MT). MT is nt as an enzyme than as a binding protein for the
cretion of phthalein dyes. Also, the hepatic accumula-
on of biliary contrast agents does not correlate with
nding to cytosolic proteins (738).
b. METALLOTHIONEIN (MT). MT

doubles BSP and bilirubin binding (758). However, con-
flicting data indicate binding to ligandin is not the sole
flows b. METALLOTHIONEIN (MT). MT is a small protein of
determinant of hepatic organic ion uptake. 1) Mutant determinant of hepatic organic ion uptake. 1) Mutant 66
Southdown sheep have impaired hepatic uptake of BSP, an
bilirubin, rose bengal, and indocyanine green yet have ma
normal concentrations of the binding proteins of liv Southdown sheep have impaired hepatic uptake of BSP, and
bilirubin, rose bengal, and indocyanine green yet have ma
normal concentrations of the binding proteins of liver ult
(217). 2) Novobiocin and probenecid interfere wi bilirubin, rose bengal, and indocyanine green yet have mormal concentrations of the binding proteins of liver u
(217). 2) Novobiocin and probenecid interfere with the obepatic uptake mechanism but do not compete with m
bil (217). 2) Novobiocin and probenecid interfere with the ochepatic uptake mechanism but do not compete with moliirubin and BSP for the binding proteins (728). 3) Little at correlation exists between the ability of microsoma hepatic uptake mechanism but do not compete with relation and BSP for the binding proteins (728). 3) Little acorrelation exists between the ability of microsomal en-
zyme inducers to enhance ligandin levels and the biliary 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 contai tion 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. 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 aro-
matic amino acids or histid 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 absorption ultra 6600 daltons that contains approximately 30% cysteine
and no cystine residues. MT does not contain any aro-
matic amino acids or histidine and hence does not absorb
ultraviolet light at 280 nm. Absorption at 250 nm does
oc 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
me matic 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 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, 5 metal-free protein, thionein, is prepared by dialyzing MT

bilirubin and BSP for the binding proteins (728). 3) Little at correlation exists between the ability of microsomal en-
zyme inducers to enhance ligandin levels and the biliary 51
excretion of chemicals (638). 4) Evans blu correlation exists between the ability of microsomal en-
zyme inducers to enhance ligandin levels and the biliary 51
excretion of chemicals (638). 4) Evans blue dye binds
appreciably to ligandin in vitro but is not readil appreciably to ligandin in vitro but is not readily taken day by the hepatocytes (728). 5) Although ligandin is riversively detectable in the liver of newborn guinea pigs, exquatake of BSP on their second day of life is co uptake of BSP on their second day of life is comparable herotothat observed in adults (1256) . 6) Hepatic uptake is bireduced in hypophysectomized and thyroidectomized bearts although ligandin is increased (981) . 7) In The ability of MT to bind metals is due to the abunat a low pH or against ethylenediaminetetraacetic (EDTA), this 250 nm absorption disappears (131, 512, 573, 676, 678, 774).
The ability of MT to bind metals is due to the a dance of cysteinyl-free sulfhydryl groups. A stoi (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 stoichiomet-

ric relationship of three mercap 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 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 hepat ric 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 be ric relationship
exists. In norm
hepatic MT is zii
bind MT, their
been determined
Concentration ists. In normal animals, the major metal bound to
patic MT is zinc (573, 574). Although numerous metals
nd MT, their actual binding affinities have not yet
en determined.
Concentration of MT in tissues can be increased by

to that observed in adults (1256). 6) Hepatic uptake is bi
reduced in hypophysectomized and thyroidectomized b
rats although ligandin is increased (981). 7) In vitro,
ligandin has a lower affinity for BSP and bilirubin tha And in has a lower affinity for BSP and bilirubin than
es albumin, yet these compounds are readily removed 127
om albumin during hepatic uptake $(364, 583, 1281)$. MT
More recent experiments demonstrate a decrease in alk
 does albumin, yet these compounds are readily removed 127
from albumin during hepatic uptake (364, 583, 1281). MT
More recent experiments demonstrate a decrease in alky
bilirubin or DBSP efflux from liver after both phenob from albumin during hepatic uptake (364, 583, 1281). M
More recent experiments demonstrate a decrease in all
bilirubin or DBSP efflux from liver after both phenobar-
uotidal-, nafenopin-, or thyroidectomy-induced increases whote recent experiments demonstrate a decrease in any is
bilirubin or DBSP efflux from liver after both phenobar-
bital-, nafenopin-, or thyroidectomy-induced increases in MT c
hepatic ligandin concentration (794, 1281, 1 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, 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). I 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 res Concentration of MT in tissues can be increased ladministration of metals such as zinc (288, 1117, 124
1271) and cadmium (288, 1072, 1242, 1272). In additio
MT can be induced in rat liver by food restriction (139
alkylatin 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 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 infecti μ and be modes in rat liver by lood restriction (159),
alkylating agents (677), stresses such as heat, cold, stren-
uous exercise, etc. (865), and bacterial infection (1108).
MT concentration in the liver of hamsters w 1000 uous 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, respectivel

26
(655). Data suggest that stress-induced increases in MT pour
concentration could be mediated by adrenal corticoste- of ca ECOM EXAMPLE 26

26 KLAASS

26 (655). Data suggest that stress-induced increases in

concentration could be mediated by adrenal cortico

coids. MT induction by metals is probably not mediated KLAASSEN AND
(655). Data suggest that stress-induced increases in MT
concentration could be mediated by adrenal corticoste-
roids. MT induction by metals is probably not mediated d
via these steroid hormones since even ver via the suggest that stress-induced increases in MT
concentration could be mediated by adrenal corticoste-
roids. MT induction by metals is probably not mediated
via these steroid hormones since even very large doses
do no (655). Data suggest that stress-induced increases in MT potentiation could be mediated by adrenal corticoste-
roids. MT induction by metals is probably not mediated do
via these steroid hormones since even very large dose concentration could
roids. MT induction
via these steroid hol
do not induce MT if
these metals (655).
The physiological ids. MT induction by metals is probably not mediated
a these steroid hormones since even very large doses
 \cdot not induce MT to the same order of magnitude as
see metals (655).
The physiological function of MT is not know

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 es 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 coppe The physiological function of MT is not known but
probably is important in the homeostasis of essential dif
trace elements, such as zinc and possibly copper (131, pat
315, 656, 668, 778, 985, 986). The function most widely probably is important in the homeostasis of essential divade elements, such as zinc and possibly copper (131, p. 315, 656, 668, 778, 985, 986). The function most widely alsudied is the ability of MT to sequester metals and trace elements, such as zinc and possibly copper $(131, 315, 656, 668, 778, 985, 986)$. The function most widely slovestudied is the ability of MT to sequester metals and metallulus reduce their toxicity $(605, 855, 1241,$ 315, 656, 668, 778, 985, 986). The function most widely sl
studied is the ability of MT to sequester metals and m
reduce their toxicity (605, 855, 1241, 1242) by binding en
metals. MT may increase their uptake into liver studied is the ability of MT to sequester metals and reduce their toxicity (605, 855, 1241, 1242) by binding enetals. MT may increase their uptake into liver in a similar manner to that originally proposed for ligandin an reduce their toxicity (605, 855, 1241, 1242) by binding er metals. MT may increase their uptake into liver in a accumulation several studies of organic anions. Indirect support for Bit this hypothesis is available from se metals. MT may increase their uptake into liver in a aci
similar manner to that originally proposed for ligandin
for the uptake of organic anions. Indirect support for Bic
this hypothesis is available from several studies. 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 for the uptake of organic anions. Indirect support for Bicarbonate ion excretion is influenced by several gas-
this hypothesis is available from several studies. A large trointestinal hormones and neural stimuli, and a po this hypothesis is available from several studies. A large the plasma to liver concentration ratio of about 30 for lead $\frac{1}{1665}$ may be due to its binding to MT. The major representation gradient for copper is also fr plasma to liver concentration ratio of about 30 for lead late (665) may be due to its binding to MT. The major reconcentration gradient for copper is also from plasma to friver and appears to be bound intracellularly to a (665) may be due to its binding to MT. The major concentration gradient for copper is also from plasma liver and appears to be bound intracellularly to a lar nondialyzable or nondiffusable protein $(628, 1169)$. The dom 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 met liver and appears to be bound intracellularly to a large solution of all and concentration gradient for mercury and meth-
dominant concentration gradient for mercury and meth-
ylmercury is also from plasma to liver (639). nondialyzable or nondiffusable protein (628, 1169). The dominant concentration gradient for mercury and meth-
ylmercury is also from plasma to liver (639). Since these
metals both bind to cytoplasmic MT and concentrate in
 ylmercury 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, pre ylmercury 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, pre metals both bind to cytoplasmic MT and concentrate i
liver, MT could facilitate hepatic uptake by sequesterin
the free metal upon entering the liver. However, pretreat
ment of rats with cadmium to induce MT does no
enhance liver, MT could facilitate hepatic uptake by sequestering and the free metal upon entering the liver. However, pretreation of rats with cadmium to induce MT does not original enhance the net uptake of cadmium, lead, arsen 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 decrease ment of rats with cadmium to induce MT does not
enhance the net uptake of cadmium, lead, arsenic, man-
ganese, copper, mercury, or zinc (649). Induction of MT
decreases the biliary excretion of cadmium over 90%,
excretion enhance the net uptake of cadmium, lead, arsenic, man-
ganese, 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%, ganese, copper, mercury, or zinc (649). Induction of M'
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 relativel
li 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, man 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, man-
ganese, and methylmercury. These results suggest and that of lead 20% (179, 193, 649). MT has relatively
little effect on the biliary excretion of arsenic, man-
ganese, and methylmercury. These results suggest MT
does not influence the plasma disappearance of metals
but little effect on the biliar ganese, and methylmercul does not influence the plate but does cause intracellular their excretion into bile.
 F Riliary Excretion *Earless, and metrymet*
does not influence the
but does cause intracell
their excretion into bile
E. Biliary Excretion
1. Classification of Ch *i* does cause intracellular sequestration and decreas
 1. Classification of Chemicals Excreted into Bile. Corn-
 1. Classification of Chemicals Excreted into Bile. Corn-
 1. Classification of Chemicals Excretion may

positive into their excretion into bile.

E. Biliary Excretion

1. Classification of Chemicals Excreted into Bile. Com-

pounds undergoing biliary excretion may be categorized

into three classes based on their bile to pla their excretion into bile.

E. Biliary Excretion

1. Classification of Chemicals Excreted into Bile. Com-

pounds undergoing biliary excretion may be categorized

into three classes based on their bile to plasma concen-

t E. Butary Excretion
1. Classification of Chemicals Excreted into Bile. Com-
pounds undergoing biliary excretion may be categorized
into three classes based on their bile to plasma concen-
tration ratios (135, 137). Class 1. Classification of Chemicals Excreted into Bile. Com-
pounds undergoing biliary excretion may be categorized
into three classes based on their bile to plasma concen-
tration ratios (135, 137). Class A substances have a pounds undergoing biliary excretion may be categorized
into three classes based on their bile to plasma concen-
tration ratios (135, 137). Class A substances have a ratio
of approximately 1.0 and include Na^+ , K^+ , $Cl^$ 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 tration ratios (135, 137). Class A substances have a r
of approximately 1.0 and include Na^{+} , K^{+} , Cl^{-} ,
glucose. Class B compounds have a bile to plasma r
usually between 10 and 1000. Examples are the bile ac
bilir of approximately 1.0 and include Na^+ , K^+ , Cl^- , and on glucose. Class B compounds have a bile to plasma ratio term usually between 10 and 1000. Examples are the bile acids, the bilirubin, BSP and other dy glucose. Class B compounds have a bile to plasma ratio ter-
usually between 10 and 1000. Examples are the bile acids, the
bilirubin, BSP and other dyes, and numerous xenobiot-
include cholesterol, phospholipids, sucrose, a usually between 10 a
bilirubin, BSP and
ics. Class C substa
include cholesterol, j
other macromolecul
Most xenobiotics Most xenobiotics for which biliary excretion is and include cholesterol, phospholipids, sucrose, albumin, and sourcher macromolecules.

Most xenobiotics for which biliary excretion is an sourcher macromolecules.

Most xeno

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 w other macromolecules.

Most xenobiotics for which biliary excretion is a

important route of elimination are class B compound

Most of the remainder of the review will be concerne

with class B compounds except for the nex Most xenobiotics for which biliary excretion is an somal
important route of elimination are class B compounds. Ano
Most of the remainder of the review will be concerned lesterc
with class B compounds except for the next fe important route of eliminaties
Most of the remainder of the with class B compounds exceptable where the biliary except
compounds will be discussed.
Little is known about the ost of the remainder of the review will be concerned let
th class B compounds except for the next few para-
haphs where the biliary excretion of class A and C le-
mpounds will be discussed. (1
Little is known about the mec

these metals (655). acid-independent fraction by active sodium ion trans-
The physiological function of MT is not known but
probably is important in the homeostasis of essential diffusion (752) with two components: a rapi KLAASSEN AND WATKINS
Pases in MT pounds of class A are excreted into bile. The distribution
corticoste- of cations in bile is similar to that in plasma as Na⁺ ion D WATKINS
pounds 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 D WATKINS
pounds 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 secret pounds 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 pounds 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 of cations in bile is similar to that in plasma as Na⁺ idominates. Passage of sodium into bile may result from a passive response to actively secreted organic anior predominantly bile acids, or the formation of the bacid 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 trans-
po a passive response to actively secreted organic anions, predominantly bile acids, or the formation of the bile predominantly bile acids, or the formation of the bile
acid-independent fraction by active sodium ion trans-
port. Potassium ion appears to reach bile only by passive
diffusion (752) with two components: a rapid one com-
p acid-independent fraction by active sodium ion transport. Potassium ion appears to reach bile only by passidiffusion (752) with two components: a rapid one conduction which the interstitial paracellular shunt and slower p port. Fotassium for appears to reach one omy by passive
diffusion (752) with two components: a rapid one com-
patible with the interstitial paracellular shunt and a
slower part which may represent transcellular K^+ move patible 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 bi slower part which may represent transcellular K^+ movement (409). Chloride ion concentration in bile is inferred by bile acid secretion (74). Species with high b acid secretion rates such as dogs (1253), rabbits (102 an ment (409). Chloride ion concentration in bile is influ-
enced 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 concentra enced by bile acid secretion (74). Species with high b
acid secretion rates such as dogs (1253), rabbits (102
and man (938) have low biliary chloride concentration
Bicarbonate ion excretion is influenced by several g
troin acid secretion rates such as dogs (1253), rabbits (1026),
and man (938) have low biliary chloride concentrations.
Bicarbonate ion excretion is influenced by several gas-
trointestinal hormones and neural stimuli, and a pos and man (938) have low biliary chloride concentration
Bicarbonate ion excretion is influenced by several g
trointestinal hormones and neural stimuli, and a post
lated canalicular bicarbonate pump (465) may be par
responsib Bicarbonate ion excretion is
trointestinal hormones and r
lated canalicular bicarbonate
responsible for elaboration o
fraction of canalicular bile.
Several lipid-insoluble sacc bintestinal hormones and neural stimuli, and a postu-
ted canalicular bicarbonate pump (465) may be partly
sponsible for elaboration of the bile acid-independent
action of canalicular bile.
Several lipid-insoluble sacchari

lated 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 simi 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 bil 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 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 , respe 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 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 als 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, 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 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 transpor In the 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 certa 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 devoi The role of microtubules and vesicular transport in t
biliary excretion of lipids is not known with certain
(1130). However, the canalicular membrane is devoid
the enzymes required for de novo synthesis of lecith
(420). Si tion. 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 pres 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 microtub (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 o tion into bile and since the biosynthetic enzymes
present in the smooth endoplasmic reticulum, the mic
tubular network appears responsible for translocation
the lipids from their site of synthesis to the canalicu
membrane present in the smooth endoplasmic reticulum, the micro-
tubular network appears responsible for translocation of
the lipids from their site of synthesis to the canalicular
membrane for excretion (419). Whether biliary lipo tubular network appears responsible for translocation of
the lipids from their site of synthesis to the canalicular
membrane for excretion (419). Whether biliary lipopro-
teins analogous to those present in plasma are invo the lipids from their site of synthesis to the canalicular
membrane for excretion (419). Whether biliary lipopro-
teins analogous to those present in plasma are involved
in biliary lipid excretion is still controversial (7 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

teins 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 impor-
tance of phospholipids and bile salts in maint in biliary lipid excretion is still controversial (773, 104
The origin of cholesterol in bile is unclear. The imp
tance of phospholipids and bile salts in maintaini
cholesterol solubility is discussed earlier in the sectio 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 cho tance of phospholipids and bile salts in maintaining
cholesterol solubility is discussed earlier in the section
on cholelithiasis. The rate of excretion of biliary choles-
terol appears independent of the rate of cholester enoiesterol solubility is uscussed earlier in the section
on cholelithiasis. The rate of excretion of biliary choles-
terol appears independent of the rate of cholesterol syn-
thesis, the level of hepatic cholesterol ester 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 (1 terol appears independent of the rate of cholesterol syn-
thesis, 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 fr thesis, the level of hepatic cholesterol ester pool, and t
amount of cholesterol absorbed from the diet (119
1191). In the rat, biliary cholesterol is derived from the
sources: 70% from plasma cholesterol, 20% newly sy
the amount of cholesterol absorbed
1191). In the rat, biliary cholester
sources: 70% from plasma chole
thesized, and 10% from an unid
somal subpool (420, 753, 1048).
Another major driving force of 91). In the rat, biliary cholesterol is derived from three urces: 70% from plasma cholesterol, 20% newly synesized, and 10% from an unidentified hepatic micromal subpool $(420, 753, 1048)$.
Another major driving

sources: 70% from plasma cholesterol, 20% newly syn-
thesized, and 10% from an unidentified hepatic micro-
somal subpool (420, 753, 1048).
Another major driving force of phospholipid and cho-
lesterol excretion into bile i the sized, 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 enteroh somal subpool (420, 753, 1048).

Another major driving force of phospholipid and cho-

lesterol excretion into bile is bile acid secretion (420).

Interruption of the enterohepatic circulation of bile acids

leads to a sub Another major driving force of phospholipid and cho-
lesterol excretion into bile is bile acid secretion (420).
Interruption of the enterohepatic circulation of bile acids
leads to a substantial decline in lipid secretion lesterol 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),

PHARMACOLOGICAL REVIEWS

aspet

BILE FORMATION, HEPATIC UI
Studies in healthy human volunteers indicate cholesterol
and phospholipid outputs are linearly coupled to bile acid BILE FORMATION, HEPATIC UPTAKE
Studies in healthy human volunteers indicate cholesterol suli
and phospholipid outputs are linearly coupled to bile acid per
secretion before and after endogenous bile acid pool in l BILE FORMATION, HEPATIC UPT.
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 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 ch Studies in healthy human volunteers indicate cholester
and phospholipid outputs are linearly coupled to bile ac
secretion before and after endogenous bile acid po
replacement (1022). The rapidity of the changes in ch
leste and phospholipid outputs are linearly coupled to bile a
secretion before and after endogenous bile acid p
replacement (1022). The rapidity of the changes in cl
lesterol and phospholipid secretion suggests that sec
tory cou secretion before and after endogenous bile acid pool in replacement (1022). The rapidity of the changes in cho-
lesterol and phospholipid secretion suggests that secre-
frory coupling of biliary lipids is altered and not b replacement (1022). The rapidity of the changes in cleaterol and phospholipid secretion suggests that sectory coupling of biliary lipids is altered and not biosy
thetic or absorptive mechanisms. Administration of t
cholere lesterol and phospholipid secretion suggests that secre-
tory coupling of biliary lipids is altered and not biosyn-
thetic or absorptive mechanisms. Administration of the
choleretic BSP causes a dose-related decrease in ch tory 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 bi thetic or absorptive mechanisms. Administration of the
choleretic BSP causes a dose-related decrease in choles-
terol and phospholipid secretion but does not affect bile
acid excretion in dogs and humans (1070). It is appa choleretic BSP causes a dose-related decrease in chole
terol and phospholipid secretion but does not affect b
acid excretion in dogs and humans (1070). It is appare
that complex physiological and physicochemical rel
tionsh 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.

that complex physiological and physicochemical rela-
tionships must be understood before a definitive mech-
anistic model can be elucidated. Sugger of the class C compounds whose excretion is poorly bra
understood include tionships must be understood before a definitive mech-
anistic model can be elucidated.
Other class C compounds whose excretion is poorly
understood include albumin, immunoglobulins, and f)
other macromolecules. Approximat anistic model can be elucidated. Summaring the class C compounds whose excretion is poorly branchers understood include albumin, immunoglobulins, and f).

other macromolecules. Approximately 80% of the protein he appearing Other class C compounds whose excretion is poorly brancher macromolecules. Approximately 80% of the protein her appearing in bile is derived from serum proteins and the sular remainder are bile-specific proteins (257, 258) mouse bile, few extrinsic canalicular enzymes (alkaline phosphatase, 5'-nucleotidase, and levels in the protein appearing in bile is derived from serum proteins and the remainder are bile-specific proteins (257, 258). In r other macromolecules. Approximately 80% of the proposaring in bile is derived from serum proteins an remainder are bile-specific proteins (257, 258). In ramouse bile, few extrinsic canalicular enzymes (all phosphatase, 5'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 naphthy 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 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 phosphatase, 5'-nucleotidase, and leucine naphthylami-
dase) can be found in bile under normal conditions (316).
These are increased during bile acid-induced choleresis,
sperhaps by detergent action of bile acids (501). Ra dase) 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 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 perhaps by detergent action of bile acids (501). Rabbrat, and guinea pig have detectable activities of alkali
phosphatase, alkaline phosphodiesterase, leucine n
phthylamidase, and lactate dehydrogenase in bile (20
394). I rat, and guinea pig have detectable activities of alkaline uliphosphatase, alkaline phosphodiesterase, leucine na-
phthylamidase, and lactate dehydrogenase in bile (207, and
394). In addition, the intact trypsin- α_2 -ma 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 thylamidase, and lactate dehydrogenase in bile (207, and
4). In addition, the intact trypsin- α_2 -macroglobulin to omplex and some degradation products are excreted into (238)
le by rats (414).
Transfer of proteins into

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 micropinocytos 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. Amyl a

holder by rats (414).

Transfer of proteins into bile is thought to occur by

bulk movement via micropinocytosis or by selective pas-

is sage through a sieving mechanism. Amylase and ribo-

houclease A in the rabbit (1 Transfer of proteins into bile is thought to occur by be
bulk movement via micropinocytosis or by selective pas-
sage through a sieving mechanism. Amylase and ribo-
hap
nuclease A in the rabbit (1001) and other ³⁵S-la bulk movement via micropinocytosis or by selective pas-
sage through a sieving mechanism. Amylase and ribo-
nuclease A in the rabbit (1001) and other ³⁵S-labeled
pancreatic proteins in the guinea pig (998) are also
secre sage through a sieving mechanism. Amylase and ribo-
nuclease A in the rabbit (1001) and other ³⁵S-labeled
pancreatic proteins in the guinea pig (998) are also
secreted into bile in significant amounts. Recent studies
(97 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, pancreatic proteins in the guinea pig (998) are also 1.0 (483, 725).
secreted into bile in significant amounts. Recent studies 2. Biliary Excretion of Cholephils. Brauer's class B
 (977) demonstrate that horseradish pe 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 vesicle (977) demonstrate that horseradish peroxidase 1) re-
mains inside membrane-limited compartments with hep-
atocytes, 2) reaches the pericanalicular cytoplasm via
evesicles 100 nm or larger in diameter, and 3) subsequently
 mains inside membrane-limited compartments with hep-
atocytes, 2) reaches the pericanalicular cytoplasm via
vesicles 100 nm or larger in diameter, and 3) subsequently
extents the biliary space by exocytosis. Similar kineti atocytes, 2) reaches the pericanalicular cytoplasm vesicles 100 nm or larger in diameter, and 3) subsequent enters the biliary space by exocytosis. Similar kine constants for hepatic uptake and biliary excretion habeen det sicles 100 nm or larger in diameter, and 3) subsequent
ters the biliary space by exocytosis. Similar kine
nstants for hepatic uptake and biliary excretion ha
en determined for four other glycoproteins (1174).
A significant enters the biliary space by exocytosis. Similar kinetic tonstants for hepatic uptake and biliary excretion have been determined for four other glycoproteins (1174).
A significant amount of the plasma-membrane-bound cenzym

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
tha been determined for four other glycoproteins (1174). and A significant amount of the plasma-membrane-bound concenzyme, 5'-nucleotidase, is found in bile (824), suggesting though that membrane fragments may break off of the 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 t that membrane fragments may break off of the vesicular po
membrane or the adjacent canalicular membrane during tre
exocytosis. However, the relevance of this mechanism to
conduction of bile or the excretion of xenobiotics 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 b exocytosis. However, the relevance of this mechanism
production of bile or the excretion of xenobiotics is
known. Insulin is another protein that normally is in
in lower concentrations than those found in plasma
477). Insu 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 rec (1171). lower concentrations than those found in plasma
7). Insulin uptake occurs by pinocytosis of recep
und hormone followed by intralysosomal degradai
171).
A technique combining cytochemistry with quant
re autoradiography (564 477). Insulin uptake occurs by pinocytosis of receptor-
bound hormone followed by intralysosomal degradation
(1171). A technique combining cytochemistry with quantita-
tive autoradiography (564, 977) has demonstrated that

bound hormone followed by intralysosomal degradation (1171).

A technique combining cytochemistry with quantita-

tive autoradiography (564, 977) has demonstrated that

within 20 minutes of injection into the portal vein,

NKE, AND BILIARY EXCRETION 27
sulin and/or metabolites appear in bile, while horseradish
peroxidase appears later. Rates of decline in appearance NKE, AND BILIARY EXCRETION 27
sulin 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 BILE FORMATION, HEPATIC UPTAKE, AND BILIARY EXCRETION 27
volunteers indicate cholesterol sulin and/or metabolites appear in bile, while horseradish
are linearly coupled to bile acid peroxidase appears later. Rates of decli sulin 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 subst sulin 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 subst 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 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 protei bile. by the sinusoidal surface directly into bile and a slow
thway involving lysosomal complexes. Both prote
we a vesicular transport mechanism for secretion in
le.
Recently, vesicular transport has also been demon-
rated for d

acid excretion in dogs and humans (1070). It is apparent strated for dimeric immunoglobulin A (IgA) and an an-
that complex physiological and physicochemical rela-
tigenically distinct glycoprotein called secretory compo-
 pathway involving lysosomal complexes. Both proteins
have a vesicular transport mechanism for secretion into
bile.
Recently, vesicular transport has also been demon-
strated for dimeric immunoglobulin A (IgA) and an an-
ti have a vesicular transport mechanism for secretion in
bile.
Recently, vesicular transport has also been demo
strated for dimeric immunoglobulin A (IgA) and an a
tigenically distinct glycoprotein called secretory comp
nent bile.
Recently, vesicular transport has also been demon-
strated for dimeric immunoglobulin A (IgA) and an an-
tigenically distinct glycoprotein called secretory compo-
nent (347, 825–829, 977, 978, 983, 1140). Additional Recently, vesicular transport has also been demoint strated for dimeric immunoglobulin A (IgA) and an altigenically distinct glycoprotein called secretory component (347, 825–829, 977, 978, 983, 1140). Additional das sugge strated 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 membr tigenically distinct glycoprotein called secretory component (347, 825–829, 977, 978, 983, 1140). Additional data
suggest that secretory component is the sinusoidal mem-
brane receptor for dimeric IgA (883) (see section VI hepatocytes of the rat (562). The ratio of the rat suggest that secretory component is the sinusoidal me brane receptor for dimeric IgA (883) (see section VI f). Uptake of IgA has also been studied in culture hepatocytes o suggest that secretory component is the shusonial mem-
brane 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 encap-
sula brane 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 encap-
sulated by endocytosis and, hence, the vesicles contain
ass f). Uptake of IgA has also been studied in cultured
hepatocytes of the rat (562) . These proteins are encap-
sulated by endocytosis and, hence, the vesicles contain
associated plasma membrane proteins. During fusion
with 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 sulated 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'-
nuc 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). with the canalicular membrane, portions of these ver
can break off and deposit secretory component an
nucleotidase into bile along with vesicular contents (
Since the glycoprotein is found free in bile, there ma
more recep 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). Immunogl 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). Immunoglob-
ulin transport from plasma to bile is very rapid (Since the glycoprotein is found free in bile, there may be
more receptors than IgA molecules (347). Immunoglob-
ulin transport from plasma to bile is very rapid (884).
IgA and IgM are concentrated in bile while IgG, albumi ulin 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 hepatocyt ulin 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
(2 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 su 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 res 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 bi (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 ha 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 be responsible in bile (214) .
haptoglobin are
and have bile to
1.0 (483, 725).
2. Biliary Ex **2.** Uptake of 1gA has also been studied in cultured

hepatocytes of the rat (562). These proteins are encap-

sulated by endocytosis and, hence, the vesicles contain

associated plasma membrane proteins. During fusion

w

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 concen 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 chole 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 impo 2. Biliary Excretion of Cholephils. Brauer's class
compounds have a bile to plasma concentration ra
greater than 1 and are referred to as cholephils. Biliar
excretion is most likely to be an important route
excretion for t 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 i 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 imp 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 conce trated in bile. However, for compounds that have loublook biological half-lives, such as methylmercury, bile can lan important route of excretion even though it is noncentrated in bile (640). Class B compounds a thought to 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 trans-
po 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 tr concentrated in bile (640). Class B compounds are
thought to be excreted by active, carrier-mediated trans-
port systems (640, 648, 1029). Classic properties of active
transport are: 1) movement of the chemical against a
c 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) substra port 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) selectivit 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 consi 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 consid saturation such that a Tm is exhibited; 3) selectivit chemical structure; and 4) the system requires expeture of energy. Although class B substances are concered to be actively transported, these four criteria rarely, if e chemical structure; and 4) the system requires expend
ture of energy. Although class B substances are consi
ered to be actively transported, these four criteria a
rarely, if ever, met. Use of inhibitors such as dinitroph
n ture 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 exc ered 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 determi nol, 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 8 KLAASSEN AND
examples will be discussed later. However, competition correction
between chemicals for biliary excretion is usually less zy
marked compared to active transport systems in kidney EXTERN AND

Examples will be discussed later. However, competition

conduction conduction conduction is usually less

compared to active transport systems in kidney

Gand intestine. The first two criteria are most commonly examples will be discussed later. However, competition c
between chemicals for biliary excretion is usually less z
marked compared to active transport systems in kidney (
and intestine. The first two criteria are most comm examples will be discussed later. However, competitie
between chemicals for biliary excretion is usually le
marked compared to active transport systems in kidn-
and intestine. The first two criteria are most common
involve 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 trans-
ported (648, 1107).
Transport maxima and high bile to p arked compared to active transport systems in kide intestine. The first two criteria are most commodived to define whether a compound is actively transport maxima and high bile to plasma concentration ratios have been demo

and intestine. The first two criteria are most commonlinvolved to define whether a compound is actively transported (648, 1107).
Transport maxima and high bile to plasma concentration ratios have been demonstrated for nume involved to define whether a compound is actively trans-
ported (648, 1107).
Transport maxima and high bile to plasma concentra-
in tion ratios have been demonstrated for numerous com-
live pounds, but these are often ambi ported (648, 1107).

Transport maxima and high bile to plasma concentra-

tion ratios have been demonstrated for numerous com-

pounds, but these are often ambiguous. Since many t

compounds undergo biotransformation duri Transport maxima and high bile to plasma concent
tion ratios have been demonstrated for numerous co
pounds, but these are often ambiguous. Since ma
compounds undergo biotransformation during passe
from plasma to bile, T_m tion ratios have been demonstrated for numerous com-
pounds, but these are often ambiguous. Since many the
compounds undergo biotransformation during passage bile
from plasma to bile, T_m 's may reflect the rate of metabpounds, 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 ra compounds undergo biotransformation during passage
from plasma to bile, T_m 's may reflect the rate of metab-
olism and not excretion. Misinterpretation of bile to
plasma ratios can occur if a compound binds to intracel-
 from plasma to bile, T_m 's may reflect the rate of metab-
olism and not excretion. Misinterpretation of bile to for its secretion into bile is not known (23, 24, 141, 289,
plasma ratios can occur if a compound binds to i olism and not excretion. Misinterpretation of bile to plasma ratios can occur if a compound binds to intracel-
lular proteins such as ligandin, intrabiliary proteins, or is sequestered within micelles. It is difficult to d plasma ratios can occur if a compound binds to intracel-
lular proteins such as ligandin, intrabiliary proteins, or
is sequestered within micelles. It is difficult to determine
as
with certainty that any chemical is active (1029). th certainty that any chemical is actively transporte
to bile. The strongest evidence available, however, if
esence of a higher concentration in bile than in plasm:
029).
Biliary excretion of endogenous and exogenous com-

into bile. The strongest evidence available, however, is with G:
presence of a higher concentration in bile than in plasma ing BS
(1029). BSP (7
Biliary excretion of endogenous and exogenous com-
compounds requires transpo presence of a higher concentration in bile than in plasma

(1029).

Biliary excretion of endogenous and exogenous com-

pounds requires transport into and out of the liver. A

obile-to-plasma concentration ratio greater th (1029).

Biliary excretion of endogenous and exogenous com

pounds requires transport into and out of the liver. ℓ

bile-to-plasma concentration ratio greater than 1.0 could

result from several possible transfer mecha Biliary excretion of endogenous and exogenous com-
pounds 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 com-
p bile-to-plasma concentration ratio greater than 1.0 coul
result from several possible transfer mechanisms. A con
pound may penetrate the sinusoidal membrane by pa
sive diffusion and enter bile by an active process; th
subs result from several possible transfer mechanisms. A con
pound may penetrate the sinusoidal membrane by pa
sive diffusion and enter bile by an active process; th
substance could be transported actively into the hep-
tocyte pound 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 t sive 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 transpor across b substance could be transported actively into the hepa-
tocyte and simply diffuse across the canalicular mem-
brane; or the chemical could undergo active transport T
across both the sinusoidal and canalicular membranes.
It selective investigation of hepaticular membranes.
It should be noted that techniques are available for
selective investigation of hepatic uptake (into intact
liver, isolated perfused liver, isolated hepatocytes, iso-
lated across both the sinusoidal and canalicular membranes. of the should be noted that techniques are available for inselective investigation of hepatic uptake (into intact a liver, isolated perfused liver, isolated hepatocytes It should be noted that techniques are available for ir selective investigation of hepatic uptake (into intact a liver, isolated perfused liver, isolated hepatocytes, iso-
lated plasma membrane vesicles) but not the excret selective investigation of hepatic uptake (into intact
liver, isolated perfused liver, isolated hepatocytes, iso-
lated plasma membrane vesicles) but not the excretory
transport step. When measuring the biliary excretion o liver, isolated perfused liver, isolated hepatocytes, i
lated plasma membrane vesicles) but not the excret
transport step. When measuring the biliary excretion
a compound, the overall production of hepatobilis
transport (u lated 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 quanti-
fie 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 a compound, the overall production of hepatobiliary
transport (uptake plus canalicular transport) is quanti-
fied. With our present state of knowledge, compounds B
can be classified into groups according to their overall d transport (uptake plus canalicular transport) is quanti-
fied. With our present state of knowledge, compounds
Bican be classified into groups according to their overall due
hepatobiliary transport characteristics without k fied. With our present state of knowledge, compound can be classified into groups according to their over-
hepatobiliary transport characteristics without knowinke cellular mechanism of transfer at each site. In spin of th can be classified into groups according to their overall duchepatobiliary transport characteristics without knowing tent
the cellular mechanism of transfer at each site. In spite the
of these limitations, it is thought tha 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 trans-
port systems are involved in excretion of chem the cellular mechanism of transfer at each site. In spite the of these limitations, it is thought that at least five trans-
port systems are involved in excretion of chemicals by vitt the liver. There are transport mechani of these limitations, it is thought that at least five trans-
port systems are involved in excretion of chemicals by
the liver. There are transport mechanisms for: 1) organic
anions such as BSP, indocyanine green, bilirubi port systems are involved in excretion of chemicals the liver. There are transport mechanisms for: 1) organ anions such as BSP, indocyanine green, bilirubin, an glucuronide conjugates; 2) bile acids; 3) organic catio-
with the liver. There are transport mechanisms for: 1) organic
anions such as BSP, indocyanine green, bilirubin, and is a
glucuronide conjugates; 2) bile acids; 3) organic cations min
with procainamide ethobromide (PAEB) as the anions such as BSP, indocyar
glucuronide conjugates; 2) bile
with procainamide ethobromic
type; 4) neutral organic compos
5) metals (32, 644, 648, 970).
a. ORGANIC ANIONS. Most c with procainamide ethobromide (PAEB) as the proto-
type; 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 mos

with procainamide ethobromide (PAEB) as the proto-
type; 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 mos type; 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 5) metals $(32, 644, 648, 970)$.

a. ORGANIC ANIONS. Most compounds are conjugated in

before excretion into bile; the most common pathways G:

are conjugation with glutathione and glucuronic acid.

Many compounds are exc a. ORGANIC ANIONS. Most compounds are conjugat
before excretion into bile; the most common pathwa
are conjugation with glutathione and glucuronic ac
Many compounds are excreted into bile at a higher ra
after conjugation pr before excretion into bile; the most common pathways G
are conjugation with glutathione and glucuronic acid. M
any compounds are excreted into bile at a higher rate
after conjugation presumably because it increases molec-
 are conjugation
Many compoun
after conjugation
ular weight and
most chemicals.
i. Conjugated Many compounds are excreted into bile at a higher rate and 20% of the maximal velocity of conjugation which after conjugation presumably because it increases molec-
after conjugation presumably because it increases molec-

D WATKINS
conjugated with the tripeptide GSH by a family of en-
zymes referred to as GSH S-transferases (549). These D WATKINS
conjugated with the tripeptide GSH by a family of en-
zymes referred to as GSH S-transferases (549). These
GSH derivatives are subsequently cleaved enzymatically D WATKINS
conjugated with the tripeptide GSH by a family of en-
zymes referred to as GSH S-transferases (549). These
GSH derivatives are subsequently cleaved enzymatically
to cysteine derivatives that may be acetylated to conjugated with the tripeptide GSH by a family of en-
zymes referred to as GSH S-transferases (549). These
GSH derivatives are subsequently cleaved enzymatically
to cysteine derivatives that may be acetylated to form
the m conjugated with the tri
zymes referred to as G
GSH derivatives are su
to cysteine derivatives
the mercapturic acid.
GSH and oxidized gl 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 lo

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 lo 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 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 h 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. E 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 regu 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 587, 588). le. Elimination of GSH and GSSG may be important
regulating hepatic levels of GSH, but the mechanism
r its secretion into bile is not known (23, 24, 141, 289,
7, 588).
Sulfobromophtalein (BSP). BSP has been used widely
a m

with certainty that any chemical is actively transported predominantly as the GSH adduct (209). Conjugation
into bile. The strongest evidence available, however, is with GSH facilitates BSP excretion into bile by produc-
p bile-to-plasma concentration ratio greater than 1.0 could metabolites into bile are much slower than their uptake
result from several possible transfer mechanisms. A com-
pound may penetrate the sinusoidal membrane by pasin 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 excre 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). Co 587, 588).

Sulfobromophtalein (BSP). BSP has been used wid

as a measure of hepatic function and is excreted into b

predominantly as the GSH adduct (209). Conjugati

with GSH facilitates BSP excretion into bile by prod
 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 produc-
ing B 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 produc-
ing BSP-GSH which has a higher excretion rate than
BSP (predominantly as the GSH adduct (209). Conjugation
with GSH facilitates BSP excretion into bile by produc-
ing BSP-GSH which has a higher excretion rate than
BSP (71, 340, 423, 1255) and by eliminating the parent
compound 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). How ing 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 metabolite 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
 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 a metabolites into bile are much slower than their uptake 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 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 i 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 (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 excreti 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 appreciable amount of extrahepatic distribution (64
The importance of GSH conjugation on biliary excretiof BSP has been demonstrated by its decreased secreti
into bile when GSH levels have been decreased by feed
a protein-The importance of GSH conjugation on biliary excret
of BSP has been demonstrated by its decreased secret
into bile when GSH levels have been decreased by feed
a protein-free diet (208), by administration of iodor
thane (94 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 iodome-
thane (946), or by diethyl maleate (1204) and by inhi a protein-free diet (208), by administration of iodome-
thane (946), or by diethyl maleate (1204) and by inhibit-
ing GSH S-transferase by benziodarone (945) or various
organic analogs of mercury, tin, and lead (152).
Rece protein-free diet (208), by administration of iodome-
ane (946), or by diethyl maleate (1204) and by inhibit-
g GSH S-transferase by benziodarone (945) or various
ganic analogs of mercury, tin, and lead (152).
Recent evide

thane (946), or by diethyl maleate (1204) and by inhibit-
ing GSH S-transferase by benziodarone (945) or various
organic analogs of mercury, tin, and lead (152).
Recent evidence further emphasizes the importance of
GSH con ing 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 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 in-
duce GSH Recent evidence further emphasizes the importance of GSH conjugation in the biliary excretion of BSP (429).
Butylated hydroxyanisole and *trans*-stilbene oxide in-
duce GSH S-transferase, increase hepatic ligandin con-
ten GSH conjugation in the biliary excretion of BSP (429).
Butylated hydroxyanisole and *trans*-stilbene oxide in-
duce GSH S-transferase, increase hepatic ligandin con-
tent, and enhance the biliary excretion of BSP. However, Butylated hydroxyanisole and *trans*-stilbene oxide in-
duce GSH S-transferase, increase hepatic ligandin con-
tent, and enhance the biliary excretion of BSP. However,
these inducers do not increase the biliary excretion o vitamin A-deficient rats (1087).

The Tm for 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 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

BSF-GSF. 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 (66 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 μ mol/min in man (1252) when BSP 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 μ mol/min in man (1252) when BSP is administered. Since BSP produces cholestasis at high d min/kg in rabbits (660), 0.14 mg/min/kg in dogs (7
660, 878), and 9.5 μ mol/min in man (1252) when BSP-
administered. Since BSP produces cholestasis at hig
doses, it is difficult to measure a true T_m (250). Studit
in 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 (105 doses, it is difficult to measure a true T_m (250). Studies 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 fo 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
 GSH into bile is energy dependent
Maximal velocity of excretion
and 20% of the maximal ve
suggests that excretion may
BSP elimination into bile.
Others. Ethacrynic acid, aximal velocity of excretion was 60% of that for uptake
d 20% of the maximal velocity of conjugation which
ggests that excretion may be the rate-limiting step in
SP elimination into bile.
Others. Ethacrynic acid, a potent suggests that excretion may be the rate-limiting step in

HARM
REV

aspet

phenobarbital increases and diethyl maleate decreases BILE FORMATION, HEPATIC UPT.
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 a GSH (178, 658). About 60% is excreted into bile within is
4 hours of administration. Pretreatment of rats with the
phenobarbital increases and diethyl maleate decreases f
the conjugation of ethacrynic acid with GSH, produc 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 simil 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
mal phenobarbital increases and diethyl maleate decreas
the conjugation of ethacrynic acid with GSH, producii
similar changes in its biliary excretion (1229). Dieth
maleate, a compound that is used experimentally to low
liver 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 excre-
tion into bile (73) .
 $ii. Conjugated with glucuronic acid.$ The most co milar changes in its biliary excretion (1229). Diethyl
aleate, a compound that is used experimentally to lower
or GSH levels, is conjugated with GSH prior to excre-
m into bile (73).
ii. *Conjugated with glucuronic acid*.

maleate, a compound that is used experimentally to lower
liver GSH levels, is conjugated with GSH prior to excre-
tion into bile (73).
ii. Conjugated with glucuronic acid. The most common
synthetic reaction produces glucur iver GSH levels, is conjugated with GSH prior to excretion into bile (73).

ii. Conjugated with glucuronic acid. The most common class

either foreign or reaction produces glucuronic acid derivatives

of various substrates bildom into bile (73).

ii. Conjugated with glucuronic acid. The most common clus

synthetic reaction produces glucuronic acid derivatives

cof various substrates, which can be either foreign or ro

endogenous compounds su ii. Conjugated with glucuronic acid. The most consynthetic reaction produces glucuronic acid derived for various substrates, which can be either foreivendogenous compounds such as steroids or bilirubinenzymes carrying out 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-glucuron-
o of various substrates, which can be either foreign or
endogenous compounds such as steroids or bilirubin. The
enzymes carrying out these reactions are UDP-glucuron-
osyltransferases, and the co-substrate is UDP-glucuronic
 endogenous compounds such as steroids or bilirubin. The
enzymes carrying out these reactions are UDP-glucuron-
osyltransferases, and the co-substrate is UDP-glucuronic
phacid. Accumulating evidence supports the hypothesis
 enzymes carrying out these reactions are UDP-glucuron-
osyltransferases, and the co-substrate is UDP-glucuronic
acid. Accumulating evidence supports the hypothesis
that there are multiple forms of this transferase, which
d yltransferases, and the co-substrate is UDP-glucuronic
id. Accumulating evidence supports the hypothesis
at there are multiple forms of this transferase, which
ffer in preferred substrate and inducibility (280, 1233).
Bili

acid. Accumulating evidence supports the hypothesis d
that there are multiple forms of this transferase, which
differ in preferred substrate and inducibility (280, 1233). c:
Bilirubin. In contrast to BSP, which is excreted that there are multiple forms of this transferase, which
differ in preferred substrate and inducibility (280, 1233). C
Bilirubin. In contrast to BSP, which is excreted pre-
alominantly as the GSH conjugate, bilirubin is ex differ in preferred substrate and inducibility (280, 1233). cre
Bilirubin. In contrast to BSP, which is excreted pre-
dominantly as the GSH conjugate, bilirubin is excreted inc
as several metabolites (335, 691) but the mos Bilirubin. In contrast to BSP, which is excreted pre-
dominantly as the GSH conjugate, bilirubin is excreted
in as several metabolites (335, 691) but the most common
are glucuronide conjugates. Excretion of bilirubin into
 dominantly as the GSH conjugate, bilirubin is excrete
as several metabolites (335, 691) but the most commo
are glucuronide conjugates. Excretion of bilirubin in
bile occurs after conjugation with either one (bilirubi
monog 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,
 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).
BM bile occurs after conjugation with either one (bilirubin iary exponsible monoglucuronide, BMG) or two (bilirubin diglucuronide, ylstilb BDG) molecules of glucuronic acid (210, 399, 1241). acid (BMG formation is catalyzed b monoglucuronide, BMG) or two (bilirubin diglucur
BDG) molecules of glucuronic acid (210, 399,
BMG formation is catalyzed by the inducible micro
enzyme UDP-glucuronosyltransferase (280, 590).
has been suggested to be produc 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 transglucuroni-
dation re BMG formation is catalyzed by the inducible microsomal
enzyme UDP-glucuronosyltransferase (280, 590). BDG (3
has been suggested to be produced by a transglucuronical
dation reaction catalyzed by bilirubin glucuronoside glu enzyme UDP-glucuronosyltransferase (280, 590). BDG
has been suggested to be produced by a transglucuroni-
dation reaction catalyzed by bilirubin glucuronoside glu-
curonosyltransferase (183, 186, 187), although other data
 has been suggested to be produced by a transglucuronication reaction catalyzed by bilirubin glucuronoside glu-
curonosyltransferase (183, 186, 187), although other data tial
suggest BDG is formed by the microsomal system (dation reaction catalyzed
curonosyltransferase (185
suggest BDG is formed b
1111). Studies on these tv
(185, 590, 1041).
In most species, biliru

suggest BDG is formed by the microsomal system $(110, 111)$. Studies on these two enzymes have been reviewed is $(185, 590, 1041)$. into In most species, bilirubin exists in bile mainly as the chemono- and the diglucuroni (185, 590, 1041). $\frac{1}{100}$ in most species, bilirubin exists in bile mainly as the chonoro- and the diglucuronides. Bilirubin excretion into hole is almost totally dependent upon conjugation as Bevidenced by the inabil (185, 590, 1041). In most species, bilirubin exists in bile mainly as the conon- and the diglucuronides. Bilirubin excretion into hile is almost totally dependent upon conjugation as Evidenced by the inability of the Gunn In most species, bilirubin exists in bile mainly as the chemono- and the diglucuronides. Bilirubin excretion into hep bile is almost totally dependent upon conjugation as BS evidenced by the inability of the Gunn rat, whi 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
e bile is almost totally dependent upon conjugation as BS
evidenced by the inability of the Gunn rat, which lacks dis
bilirubin UDP-glucuronosyltransferase, to conjugate and an
excrete bilirubin while having normal T_m for evidenced by the inability of the Gunn rat, which lacks dis
bilirubin UDP-glucuronosyltransferase, to conjugate and an
excrete bilirubin while having normal T_m for conjugated tion
bilirubin (42). In addition, the amount 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. C excrete bilirubin while having normal T_m for conjuga
bilirubin (42). In addition, the amount of BMG in bil
higher and BDG lower in conditions associated w
deficient UDP-glucuronosyltransferase activity, e.g. (
gler-Najj 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. Cri-
gler-Najjar disease, Gilbert's syndrome, and heterozy-
 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-depende deficient UDP-glucuronosyltransferase activity, e.g. Crimator biotransformed before excretion (181, 521, 1248).
gler-Najjar disease, Gilbert's syndrome, and heterozy-
gous Gunn rats (111, 335, 397, 403, 1237). The excreto gous Gunn rats (111, 335, 397, 403, 1237). The excretory a correspondent ranging from 39 μ g/min/kg in man (1194) to 610 in address (991, 1243). These large species variations may relate tic differences in hepatic conju transport maximum for bilirubin is also species-depent ranging from $39 \mu g/min/kg$ in man (1194) to 6 rats (991, 1243). These large species variations may r to differences in hepatic conjugating capacity, such activity of bili ent ranging from 39 μ g/min/kg in man (1194) to 610 in adments (991, 1243). These large species variations may relate tion
to differences in hepatic conjugating capacity, such as ICC
the activity of bilirubin UDP-glucur rats (991, 1243). These large species variations ma
to differences in hepatic conjugating capacity, i
the activity of bilirubin UDP-glucuronosyltran
(335, 433). Maximal biliary secretion of bilirub
bile appears to be very to differences in hepatic conjugating capacity, such the activity of bilirubin UDP-glucuronosyltransfera (335, 433). Maximal biliary secretion of bilirubin in bile appears to be very dependent on UDP-glucuronosy transferas the activity of bilirubin UDP-glucuronosyltransferase (335, 433). Maximal biliary secretion of bilirubin into bile appears to be very dependent on UDP-glucuronosyl-transferase activity (1203). Moreover, depletion of UDP-gl (335, 433). Maximal biliary secretion of bilirubin into
bile appears to be very dependent on UDP-glucuronosyl-
transferase activity (1203). Moreover, depletion of UDP-
glucuronic acid in liver by galactosamine or diethyl e bile appears to
transferase ac
glucuronic aci
decreases the
rubin (433).
Bilirubin is ansferase activity (1203). Moreover, depletion of UDP-
ncuronic acid in liver by galactosamine or diethyl ether
creases the conjugation and biliary excretion of bili-
models of the choler of the Bilirubin is not a choleret decreases the conjugation and biliary excretion of bili-
rubin (433).
Bilirubin is not a choleretic. In sheep during a state of
maximal bilirubin excretion, bile flow rate and osmolar-

BILE FORMATION, HEPATIC UPTAKE, AND BILIARY EXCRETION **BILIARY EXCRETION** 29
GSH (178, 658). About 60% is excreted into bile within ity are not changed while biliary sodium ion concentra-4 hours of administration. Pretreatment of rats with tion increases (77). Since no change in osmolarity or bile
phenobarbital increases and diethyl maleate decreases flow occurs with the increased biliary bilirubin concen-IKE, AND BILIARY EXCRETION
ity are not changed while biliary sodium ion concention increases (77). Since no change in osmolarity or KE, AND BILIARY EXCRETION 29
ity are not changed while biliary sodium ion concentra-
tion increases (77). Since no change in osmolarity or bile
flow occurs with the increased biliary bilirubin concen-KE, AND BILIARY EXCRETION
ity are not changed while biliary sodium ion concent
tion increases (77). Since no change in osmolarity or t
flow occurs with the increased biliary bilirubin conc
tration, bilirubin may associate ity 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 o ity 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 o tion increases (77). Sin
flow occurs with the ir
tration, bilirubin may
form molecular aggrega
of the biliary bilirubin.
Others. Many, if not w occurs with the increased biliary bilirubin concention, bilirubin may associate with mixed micelles or m molecular aggregates and mask the osmotic activity the biliary bilirubin.
Others. Many, if not most, compounds excr

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 in-
clude the uricosuric agent probene dude the biliary bilirubin.

Others. Many, if not most, compounds excreted into

bile are conjugated with glucuronic acid. Examples in-

clude the uricosuric agent probenecid (439), the biliary

contrast agent iopanoate (2 Others. Many, if not most, compounds excreted if the are conjugated with glucuronic acid. Examples clude the uricosuric agent probenecid (439), the bilicontrast agent iopanoate (211–213), the synthetic roid, diethylstilbes bile are conjugated with glucuronic acid. Examples in-
clude the uricosuric agent probenecid (439), the biliary
contrast agent iopanoate (211–213), the synthetic ste-
roid, diethylstilbestrol (627), the disinfectant hexach clude the uricosuric agent probenecid (439), the biliary
contrast agent iopanoate (211–213), the synthetic ste-
roid, diethylstilbestrol (627), the disinfectant hexachlo-
rophene (379, 653), the anticonvulsant valproic aci contrast agent iopanoate (211–213), the synthetic steroid, diethylstilbestrol (627), the disinfectant hexachlo-
rophene (379, 653), the anticonvulsant valproic acid (252,
253, 1234, 1236), the dyes phenolphthalein (199), roid, diethylstilbestrol (627), the disinfectant hexachlorophene (379, 653), the anticonvulsant valproic acid (252, 253, 1234, 1236), the dyes phenolphthalein (199), and phenolsulfonphthalein (phenol red) (467), fluoresce phene (379, 653), the anticonvulsant valproic acid (252, 3, 1234, 1236), the dyes phenolphthalein (199), and enolsulfonphthalein (phenol red) (467), fluorescein es (1240), vitamin D_3 (745), and thyroxine (349, 395). Th

phenolsulfonphthalein (phenol red) (467), fluorescein
dyes (1240), vitamin D_3 (745), and thyroxine (349, 395).
The importance of glucuronidation on the biliary ex-
cretion of a number of compounds is emphasized by the
 phenolsulfonphthalein (phenol red) (467) , fluorescein
dyes (1240) , vitamin D₃ (745) , and thyroxine $(349, 395)$.
The importance of glucuronidation on the biliary ex-
cretion of a number of compounds is emphasized dyes (1240), vitalini D_3 (140), and thyroxine (343, 350).
The importance of glucuronidation on the biliary ex-
cretion of a number of compounds is emphasized by the
alteration in biliary excretion that is observed after cretion 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-
methy alteration in biliary excretion that is observed after a
increase or decrease in glucuronidation. Induction
UDP-glucuronosyltransferase by phenobarbital or
methylcholanthrene has been shown to enhance the b
iary excretion increase or decrease in glucuronidation. Induction of UDP-glucuronosyltransferase by phenobarbital or 3-
methylcholanthrene has been shown to enhance the bil-
iary excretion of thyroxine (349), iopanoate (211), dieth-
ylst UDP-glucuronosyltransferase by phenobarbital of methylcholanthrene has been shown to enhance the inty excretion of thyroxine (349), iopanoate (211), dylstilbestrol (627), hexachlorophene (653), and valy acid (1236). Howeve methydronalthrene has been shown to emlance the bh-
iary excretion of thyroxine (349), iopanoate (211), dieth-
ylstilbestrol (627), hexachlorophene (653), and valproic
acid (1236). However, enhancement of the glucuronida-
 ylstilbestrol (627), hexachlorophene (653), and valproic
acid (1236). However, enhancement of the glucuronida-
tion of morphine does not increase its excretion into bile
(373, 534, 910). Depression of UDP-glucuronic acid c acid (1236). However, enhancement of the glucuronid
tion of morphine does not increase its excretion into bi
(373, 534, 910). Depression of UDP-glucuronic acid co
centrations by galactosamine or diethyl ether has be
shown tion of morphine does not increase its excretion into 1 (373, 534, 910). Depression of UDP-glucuronic acid contrations by galactosamine or diethyl ether has behown to decrease the glucuronidation and biliary excession of d (373, 534, 910). Depression of UDP-centrations by galactosamine or die
shown to decrease the glucuronidation
tion of diethylstilbestrol, valproic ac
and iopanoic acid (213, 433, 1236).
iii. Not Biotransformed. Several ch ntrations by galactosamine or diethyl ether has been
own to decrease the glucuronidation and biliary excre-
on of diethylstilbestrol, valproic acid, phenolphthalein,
d iopanoic acid (213, 433, 1236).
iii. *Not Biotransform*

suggest BDG is formed by the microsomal system $(110, 111)$. Studies on these two enzymes have been reviewed iii. Not Biotransformed. Several chemicals are excreted $(185, 590, 1041)$.

into bile without prior biotransfor into 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 t tion 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 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 excretor 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. into bile without prior biotransformation. Some of the effection is a seed diagnostically to determine patic excretory function in man similar to that is BSP. These chemicals have been extremely useful dissecting the effec chemicals have been used diagnostically to determin
hepatic excretory function in man similar to that for
BSP. These chemicals have been extremely useful is
dissecting the effect that physiological, pharmacologica
and toxi tion. SP. These chemicals have been extremely useful in
secting the effect that physiological, pharmacological,
d toxicological factors have on hepatic excretory func-
n.
Indocyanine Green (ICG). ICG is used clinically to
easure

dissecting the effect that physiological, pharmacological,
and toxicological factors have on hepatic excretory func-
tion.
Indocyanine Green (ICG). ICG is used clinically to
measure both cardiac output and hepatic function 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, 124 tion.

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, f 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 onemeasure 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
de not biotransformed before excretion (181, 521, 124
Clearance of ICG from plasma, in contrast to BSP,
a one-compartment open model and its half-life is v
dependent on dose (664) in the first 20 minutes at
administration. H Clearance of ICG from plasma, in contrast to BSF, its
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 elimina-
tio dependent on dose (664) in the first 20 minutes after
administration. However, at longer times, ICG elimina-
tion is non-linear (1141). It is difficult to obtain a T_m for
ICG because of its cholestatic properties (507, 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 μ moles/min tion 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 μ moles/min/kg) is much faster than its excretion into bile (0.2 ICG because of its cholestatic properties $(507, 508$
Removal of ICG from plasma $(3.8 \mu moles/min/much$ faster than its excretion into bile $(0.244 \mu minn/kg)$ in rats $(901, 902)$. Biliary excretion of IC rose bengal depends on bile a expressed of ICG from plasma $(3.8 \mu \text{moles/min/kg})$ is
uch faster than its excretion into bile $(0.244 \mu \text{moles/m/kg})$ in rats $(901, 902)$. Biliary excretion of ICG and
se bengal depends on bile acid excretion (427) .
Rose Bengal.

much faster than its excretion into bile $(0.244 \mu m o \text{les/m} \text{m} \text{m} \text{m} / \text{kg})$ in rats (901, 902). Biliary excretion of ICG and rose bengal depends on bile acid excretion (427).
Rose Bengal. Rose bengal has been used cl 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 be-
fore ex rose bengal depends on bile acid excretion (427).
Rose Bengal. Rose bengal has been used clinically to
measure hepatic function and is not biotransformed be-
fore excretion (343, 559, 690). It exhibits a rapid and
biphasic measure hepatic function and is not biotransformed be-
fore 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 s

PHARMACOLOGICAL REVIEWS

at 100 mg/kg. Rose bengal concentrates in liver and creappears to be bound to proteins other than ligandin (646). che SO
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 SO

Solution the transport maximum for rose bengal into bile of rats

The transport maximum for rose bengal into bile of rats

is $100 \mu g/min/kg (646)$. at 100 mg/kg. Rose ber
appears to be bound to pro
The transport maximum
is 100 μ g/min/kg (646).
Phenol-3,6-Dibrompht appears to be bound to proteins other than ligandin (646).
The transport maximum for rose bengal into bile of rats
is $100 \mu g/min/kg$ (646).
Phenol-3,6-Dibromphthalein Disulfonate (DBSP).
DBSP is the dibrominated analog of BSP

appears to be bound to proteins other than ligandin (64
The transport maximum for rose bengal into bile of re
is $100 \mu g/min/kg$ (646).
Phenol-3,6-Dibromphthalein Disulfonate (DBSI
DBSP is the dibrominated analog of BSP, is no is 100 μ g/min/kg (646).

is 100 μ g/min/kg (646).

Phenol-3,6-Dibromphthalein Disulfonate (DBSP). Bile

DBSP is the dibrominated analog of BSP, is not conju-

gated before excretion (553), and is handled by the liver Phenor-3,0-Dioromphinatem Disurbonate (DBSP).
DBSP is the dibrominated analog of BSP, is not conju-
gated before excretion (553), and is handled by the liver re
in a similar manner to BSP. The disappearance from ce
plasma, DBSP is the dibrominated analog of BSP, is not conju-
gated before excretion (553), and is handled by the liver
in a similar manner to BSP. The disappearance from
cent
plasma, storage in liver, and excretion into bile are gated before excretion (553), and is handled by the liver red
in a similar manner to BSP. The disappearance from cer
plasma, storage in liver, and excretion into bile are oth
similar for both dyes in rats, rabbits, and do in a similar manner to BSP. The disappearance fro
plasma, storage in liver, and excretion into bile a
similar for both dyes in rats, rabbits, and dogs (662).
humans, the plasma disappearance and storage of DBS
is somewhat plasma, storage in 1
similar for both dyes
humans, the plasma d
is somewhat greater t
tion is similar (249).
Others. Several oth minar for both dyes in rats, rabbits, and dogs (002). I
mans, the plasma disappearance and storage of DBS
somewhat greater than for BSP but the T_m for excret
in is similar (249).
Others. Several other dyes are excreted

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), brom is somewhat greater than for BSP but the T_m for excretion is similar (249).

Others. Several other dyes are excreted into bile wit

out being biotransformed. Amaranth (red dye no. 2) (53

1012, 1018), eosine (1040), bro tion is similar (249).

Others. Several other dyes are excreted into bile wit

out being biotransformed. Amaranth (red dye no. 2) (5

1012, 1018), eosine (1040), bromcresol green (200), ch

rothiazide (466), succinylsulfat Others. Several other dyes are excreted into bile with-
out being biotransformed. Amaranth (red dye no. 2) (531,
1012, 1018), eosine (1040), bromcresol green (200), chlo-
rothiazide (466), succinylsulfathiazole (809), and out being biotransformed. Amaranth (red dye no. 2)
1012, 1018), eosine (1040), bromcresol green (200), or
rothiazide (466), succinylsulfathiazole (809), and ta
zine (100) are pertinent examples. However, more revidence ind notz, 1018), eosine (1040), broincresor green (200), cino-
rothiazide (466), succinylsulfathiazole (809), and tartra-
zine (100) are pertinent examples. However, more recent
evidence indicates amaranth does undergo biotran zine (100) are pertinent exam
evidence indicates amaranth
mation (1012). Further word
whether any other of these "r
are biotransformed as well.
b. BILE ACIDS. Originally, idence indicates amaranth does undergo biotransfor-
ation (1012). Further work is needed to ascertain effecti
nether any other of these "non-metabolized" chemicals protec
e biotransformed as well.
b. BILE ACIDS. Originally

mation (1012). Further work is needed to ascertain e
whether any other of these "non-metabolized" chemicals p
are biotransformed as well.
b. BILE ACIDS. Originally, a common carrier system p
was postulated for the biliary are biotransformed as well.

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 mutan b. BLE ACIDS. Originally, a common carrier system
was postulated for the biliary excretion of all organi
acids. Then, Alpert et al. (32) demonstrated that mutar
Corriedale sheep were unable to excrete BSP, iopanoi
acid, ph 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 inca Corriedale sheep were unable to excrete BSP, iopanoic
acid, phylloerythrin, conjugated bilirubin, etc. but elim-
inated bile acids normally via the bile. Although incap-
able of excreting BSP-GSH, Corridale sheep secrete u acid, phynoerythmi, conjugated billioni, etc. but emil-
inated bile acids normally via the bile. Although incap-
able of excreting BSP-GSH, Corridale sheep secrete un-
conjugated BSP at a lower rate than normal ewes (76).
 inated 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 able 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 en-
hance conjugated BSP at a lower rate than normal ewes (76). check further support for independent carriers was obtained do
by the observations that phenobarbital pretreatment energies the biliary excretion of BSP and DBSP but no Further support for independent carriers was obtained
by the observations that phenobarbital pretreatment en-
hances the biliary excretion of BSP and DBSP but not
taurocholate (620, 663, 900), that indocyanine green has
no by the observations that phenobarbital pretreatment en-
hances the biliary excretion of BSP and DBSP but not
taurocholate (620, 663, 900), that indocyanine green has
plno effect on taurocholate uptake into the isolated per hances 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 bi 791).

 10% free in the cytosol (1145, 1146). The rate-limiting 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, 114 791).
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, 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 $(393, 39$ cytosolic proteins and subcellular organelles with 1% to mail 10% free in the cytosol (1145, 1146). The rate-limiting PA step in the excretion of bile acids (393, 398, 970) is their experiment across the canalicular membr To *n* lies in the cytosof (1140, 1140). The face-initially
step in the excretion of bile acids (393, 398, 970) is their
transport across the canalicular membrane which ap-
pears to be a saturable process and is character step in the excretion of bile acids (393, 398, 970) is their extransport across the canalicular membrane which ap-
pears to be a saturable process and is characterized by a p
T_m under steady-state conditions (obtained b transport across the canalicular membrane which ap-
pears to be a saturable process and is characterized by a
plase T_m under steady-state conditions (obtained by stepwise after
increased infusions of bile acids). Report Sears to be a saturable process and is characterized by a
 Γ_m under steady-state conditions (obtained by stepwise

ncreased infusions of bile acids). Reported T_m values for

caurocholate are 14.2 μ mol/min/kg in sh T_m under steady-state conditions (obtained by stepwise after administration of sulfhydryl reagents intraportally increased infusions of bile acids). Reported T_m values for or via intrabiliary infusion indicates that p increased infusions of bile acids). Reported T_m values for o
taurocholate are 14.2 μ mol/min/kg in sheep (473), 8.5 c
 μ mol/min/kg in dogs (874), and 13 μ mol/min/kg in rats o
(14, 398, 904). Biliary transport is triangle are 14.2 μ mol/min/kg in sheep (475), 6.5
 μ mol/min/kg in dogs (874), and 13 μ mol/min/kg in rats

(14, 398, 904). Biliary transport is more efficient for

conjugated bile acids than unconjugated analogs, (971). 4, 398, 904). Biliary transport is more efficient for nivigated bile acids than unconjugated analogs, and for hydroxy bile acids than that of dihydroxy bile acids 71).
However, maximal bile acid secretion for individual le

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 trihydroxy bile acids than that of dihydroxy bile aci
(971).
However, maximal bile acid secretion for individualitie acids also depends on the toxicity of each acident
Recent data obtained in rats indicate the maximal secr 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 secre-
tion rate decreases as the toxicity of the bile acid inD WATKINS
creases (462). Maximal excretion of nontoxic taurour
chenodeoxycholate was about 55 μ mol/min/kg or D WATKINS
creases (462). Maximal excretion of nontoxic taurourso-
chenodeoxycholate was about 55 μ mol/min/kg or 2.5
times higher than that of taurocholate. Similar results D WATKINS
creases (462). Maximal excretion of nontoxic taurourso-
chenodeoxycholate was about 55 μ mol/min/kg or 2.5
times higher than that of taurocholate. Similar results
have been observed by others (264, 611). creases (462). Maximal excretion of nontc
chenodeoxycholate was about 55 μ mol/i
times higher than that of taurocholate. S
have been observed by others (264, 611).
Bile acid transport depends on maintena beases (402). Maximal excretion of nontoxic taurourso-
enodeoxycholate was about 55 μ mol/min/kg or 2.5
nes higher than that of taurocholate. Similar results
we been observed by others (264, 611).
Bile acid transport de

chemodeoxycholate was about 35 μ mol/min/kg or 2.3
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 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 hepatocyte 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 orga 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
cell cells (1120). Adaptation to selective biliary obstruction 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 obstruct 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 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 manifes 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. T 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
pl 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
indi 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
st 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
uptak 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
 murectly by cycloneximide (356) 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 protein. fective enterohepatic circulation of bile acids while
otecting the peripheral circulation from high bile acid
ncentrations and removing the need for a major storage
otein.
c. ORGANIC CATIONS. Evidence for an active excreto

no effect on taurocholate uptake into the isolated per-
fused rat liver (902), and that nafenopin decreases the
biliary excretion of organic acids but not bile acids (790, urable uptake and excretory processes (834). Addi 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 organi 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 mo 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). Furthe 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 ind system at the canalicular membrane for organic base
the reported bile/liver ratios of 10 or more for total PA
in the rat (518, 792, 835, 1031). Further studies indic
that several organic bases which are excreted into \vert
 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 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 dehydro-
cholate, enhances PAEB elimination into bile, but PA that several organic bases which are excreted into bile
inhibit PAEB secretion. Taurocholate, but not dehydro-
cholate, enhances PAEB elimination into bile, but PAEB
does not affect taurocholate excretion (694, 1031). Thes mmont FAEB secretion. I aurocholate, but not denyaro-
cholate, 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
ch does not affect taurocholate excretion (694, 1031). Theffects are not due to binding to micelles (1213) choleresis (694). Isopropamide iodide decreases the livel plasma ratio for PAEB and its biliary excretion (8; Similar effects are not due to binding to micenes (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 procain-
a plasma ratio for PAEB and its biliary excretion (835).
Similar results have been observed for acetyl procain-
amide ethobromide (acetyl-PAEB) (837) which has sat-
urable uptake and excretory processes (834). Additional
stu Similar results have been observed for acetyl p
amide ethobromide (acetyl-PAEB) (837) which h
urable uptake and excretory processes (834). Add
studies indicate that retrograde intrabiliary infu
the fluorescent probe N-[p-(amide ethobromide (acetyl-PAEB) (837) which has surable uptake and excretory processes (834). Addition
studies indicate that retrograde intrabiliary infusion
the fluorescent probe N-[p-(2-benzimidazolyl)phen
maleimide redu urable 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 acety 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
ex 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 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/
pla exposed sulfhydryl groups on the carrier protein can
inhibit cation excretion into bile. Comparison of liver/
plasma concentration ratios of PAEB and acetyl-PAEB exposed sulfhydryl groups on the carrier protein
inhibit cation excretion into bile. Comparison of l
plasma concentration ratios of PAEB and acetyl-P
after administration of sulfhydryl reagents intrapol
or via intrabiliary 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-chloromer plasma concentration ratios of PAEB and acetyl-PAE
after administration of sulfhydryl reagents intraportal
or via intrabiliary infusion indicates that *p*-chlorome
curibenzoate and iodoacetamide inhibit hepatic uptal
of th after administration of sulfhydryl reagents intraportally
or via intrabiliary infusion indicates that p -chloromer-
curibenzoate and iodoacetamide inhibit hepatic uptake
of the cations, N-ethylmaleimide decreases only ex or via intrabiliary infusion indicates that *p*-chloromer-
curibenzoate and iodoacetamide inhibit hepatic uptake
of the cations, N-ethylmaleimide decreases only excre-
tion, and *p*-chloromercury phenyl sulfonic acid inhib curibenzoate and iodoacetamide inhibit hepatic uptake
of the cations, N-ethylmaleimide decreases only excre-
tion, and p-chloromercury phenyl sulfonic acid inhibits
both steps. Thus, these authors suggest that exposed
sulf of the cations, N-ethylmaleimide decreation, and p-chloromercury phenyl sulfor
both steps. Thus, these authors sugges
sulfhydryl groups appear to be present
and excretory transport systems (833).
The structural requirement on, and p-chloromercury phenyl sulfonic acid inhibits
th steps. Thus, these authors suggest that exposed
lfhydryl groups appear to be present on both uptake
d excretory transport systems (833).
The structural requirements sulfhydryl groups appear to be present on both uptake
and excretory transport systems (833).
The structural requirements for transport by the or-
ganic cation pathway are a basic amino group on one

sumiyaryi groups appear to be present on both uptake
and excretory transport systems (833).
The structural requirements for transport by the or-
ganic cation pathway are a basic amino group on one
side of the molecule and

PHARMACOLOGICAL REVIEWS

BILE FORMATION, HEPATIC UPTAKE, AND BILIARY EXCRETION
640). Several bis-onium compounds including d-tubocu-retained in the body for a long
rarine and hexafluorenium appear to be actively trans-compounds, some metals ine BILE FORMATION, HEPATIC
640). Several bis-onium compounds including *d*-tuboc
rarine and hexafluorenium appear to be actively trans
ported from plasma to bile (787, 788, 792, 793, 796–798 BILE FORMATION, HEPATIC U
640). Several bis-onium compounds including d-tubocu-
rarine and hexafluorenium appear to be actively trans-
ported from plasma to bile (787, 788, 792, 793, 796-798)
In spite of marked physicochem 640). Several bis-onium compounds including d -tubo
rarine and hexafluorenium appear to be actively tra
ported from plasma to bile (787, 788, 792, 793, 796–79
In spite of marked physicochemical differences, thiaz
amium a 640). Several bis-onium compounds including d-tubocu-
rarine and hexafluorenium appear to be actively trans-
ported from plasma to bile (787, 788, 792, 793, 796–798).
In spite of marked physicochemical differences, thiazi rarine and hexafluorenium appear to be actively trans-
ported from plasma to bile (787, 788, 792, 793, 796–798). mere
In spite of marked physicochemical differences, thiazin-
bile
amium and its sulfoxide analog differ sli 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 chloroguan amium and its sulfoxide analog differ slightly in hepatic ide-triazine in vivo (839). However, transport of bisquar-
ternary compounds is decreased by K-strophanthoside
while that of PAEB is not (792). This effect is due to uptake and biliary excretion (842). A similar mechanism pati
has been determined for the tertiary amine chloroguan-
ide-triazine in vivo (839). However, transport of bisquar-
iternary compounds is decreased by K-strophanth has been determined for the tertiary amine chloroguan-
ide-triazine in vivo (839). However, transport of bisquar-
ternary compounds is decreased by K-strophanthoside
while that of PAEB is not (792). This effect is due to
o ide-triazine in vivo (839). However, transport of bisquar-
ternary 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
 while that of PA
depression of up
bisquaternary c
(788, 793, 798).
d. NEUTRAL depression of uptake by interfering with binding of the vertical depression of uptake by interfering with binding of the vertical organization (788, 793, 798).

(788, 793, 798).

(288, 793, 798).

(288, 793, 798).

(288, 7

bisquaternary compounds to intracellular organelles

(788, 793, 798).

d. NEUTRAL ORGANIC CHEMICALS. Two classes of

chemicals eliminated via this system are monosaccha

rides and neutral steroids. Under normal physiologic (788, 793, 798).
d. NEUTRAL ORGANIC CHEMICALS. Two classes of
chemicals eliminated via this system are monosaccha-
rides and neutral steroids. Under normal physiological
conditions few mono- or oligosaccharides enter bile. d. NEUTRAL ORGANIC CHEMICALS. Two classes of 1
chemicals eliminated via this system are monosaccha-
rides and neutral steroids. Under normal physiological to
conditions few mono- or oligosaccharides enter bile. Glu-
cose a chemicals eliminated via this system are monosaccharides and neutral steroids. Under normal physiological conditions few mono- or oligosaccharides enter bile. Glu-cose appears in human bile only when the plasma glucose con rides and neutral steroids. Under normal physiological talconditions few mono- or oligosaccharides enter bile. Glu-
cose appears in human bile only when the plasma glucose into
concentration exceeds 350 mg/dl (970). In the conditions few mono- or oligosaccharides enter bile. Glucase appears in human bile only when the plasma glucose is concentration exceeds $350 \text{ mg}/\text{dl}$ (970). In the rat, glucose is reabsorbed from bile into liver and li cose appears in human bile only when the plasma glucose in
concentration exceeds 350 mg/dl (970). In the rat, glu-
cose is reabsorbed from bile into liver and little is found
in bile until the plasma glucose concentration concentration exceeds 350 mg/dl (970). In the rat, $\frac{1}{100}$ cose is reabsorbed from bile into liver and little is for in bile until the plasma glucose concentration exce 280 mg/dl. This can be blocked by phlorizin, a s cose is reabsorbed from bile into liver and little is found
in bile until the plasma glucose concentration exceeds incr
280 mg/dl. This can be blocked by phlorizin, a specific but
inhibitor of glucose transport (447). Gluc 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 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 (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 s tion 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 rema using th
(872). He
system w
to be esta
in bile.
The se 72). However, localization of this specific transport interesting which prevents loss of glucose via the bile remains plate the second class of neutral compounds include the bile. The second class of neutral compounds inc 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.

to be established. No sugar is known to be concentrated complements in bile.

The second class of neutral compounds include the b

endogenous steroid hormones and cardiac glycosides. We

The prototype of this class is ouab gr The second class of neutral compounds include the biotrophogenous steroid hormones and cardiac glycosides. we
The prototype of this class is ouabain. This cardiac dataly
glycoside is not biotransformed (219, 696) before The second class of neutral compounds include the bile endogenous steroid hormones and cardiac glycosides. weight the prototype of this class is ouabain. This cardiac dalt glycoside is not biotransformed (219, 696) before endogenous steroid hormones and cardiac glycosides. weight The prototype of this class is ouabain. This cardiac dalt glycoside is not biotransformed (219, 696) before its circ excretion. Ouabain also does not appear to be The prototype of this class is ouabain. This cardiac dalt glycoside is not biotransformed (219, 696) before its circ
excretion. Ouabain also does not appear to be bound to ii.
components of liver homogenates (696) or liga 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 minu 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 components of liver homogenates (696) or ligandin
particular (638). The bile/liver concentration ratio
minutes after administration is 70 which suggests of
bain may be excreted by an active mechanism (10
Although ouabain i minutes after administration is 70 which suggests oua-
bain may be excreted by an active mechanism (1016). in urine (112). When lead was similarly administered to
Although ouabain is tightly bound to micelles, taurocho-
l bain may be excreted by an active mechanism (1016). of ouabain in bile (1216).

late administration does not affect its biliary excretion wand cannot account for the concentrative accumulation in of ouabain in bile (1216). h
Biliary excretion of endogenous estrogens varies from d
20% to 60% depending 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 excretio 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 conjugate Binary excretion of endogenous estiogens 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, sulf clear, these hormones are conjugated with glucuronic mal amounts thereafter (665). Most of the lead excreted acid, sulfate, or glucosiduronate (698, 1168) and thus into feces is via bile (112, 190). In humans, urine appea might be excreted by the organic anion transport system. 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 digi-
t might be excreted by the organic anion transport system. to
However, in rats steroids appear to be excreted by the
same pathway as ouabain (412, 696). Digoxin and digi-
intoxin may be excreted by the ouabain pathway; howev 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 e. Metalway as buabann (412, 050). Digoxin and digi-
in may be excreted by the ouabain pathway; however, a
nce they are glucuronidated before excretion they are
obably secreted by the organic acid pathway.
for heavy metals

be excreted by the budden pathway, however, according to the past decade and pathway. If the past decade and planet and been studied systematically only in the past decade and planet has been reviewed (644). Although many

RE, AND BILIARY EXCRETION 31
Tetained in the body for a longer time than most organic
compounds, some metals including lead, manganese, KE, AND BILIARY EXCRETION 33
retained in the body for a longer time than most organic
compounds, some metals including lead, manganese
mercury, copper, zinc, and cadmium are excreted inte ME, AND BILIARY EXCRETION 31
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 int retained in the body for a longer time the
compounds, some metals including les
mercury, copper, zinc, and cadmium ar
bile to a greater extent than into urine.
i. Copper. More work has been condu relation of the body for a longer time than most organic mpounds, some metals including lead, manganese, ercury, copper, zinc, and cadmium are excreted into the to a greater extent than into urine.
i. Copper. More work h

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 he-
patic disposition of co bile to a greater extent than into urine.
 $i. Copper. More work has been conducted on the he-
patic disposition of copper than with the other metals
because of attempts to characterize abnormal metabolism in patients with Wilson's disease (hepatolenticular$ bile to a greater extent than into urine.
 i. Copper. More work has been conducted on the heatic disposition of copper than with the other meta

because of attempts to characterize abnormal metabolism in patients with W degeneration) (1019, 1136). The main route for excretion
degeneration) (1019, 1136). The main route for excretion
of copper is via the feces. Rats excrete 20% of an intra-
venous dose of copper in the feces within 24 hours because of attempts to characterize abnormal metabo-
lism 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 intr lism 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 hou degeneration) (1019, 1136). The main route for excretion
of copper is via the feces. Rats excrete 20% of an intra-
venous dose of copper in the feces within 24 hours and
only 6% in urine (888). When administered to humans 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 when as dose of copper in the lects 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, co

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 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 live 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
i 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 $1 \text{ mg/kg$

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 $1 \text{ mg/kg$ into ceruloplasmin and secreted into plasma (890, 891
The excretion of copper into bile has been shown
increase with increasing dose in the rat up to 1 mg/
but not at 3 mg/kg (628). This suggests that a transpor
maximum f 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 excre-
tion netease with increasing dose in the rat up to 1 mg/ss
but not at 3 mg/kg (628). This suggests that a transport
maximum for copper has been reached, although excre-
tion may be limited by copper toxicity since 3 mg/kg is
n 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 i 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/ pl tion 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 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 bi 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 int 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 molecula 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 d gradient is quite s
bile of rats is assot
weight substances
dalton protein is
circulation (369).
ii. Lead. Lead is ¹ ight substances (194). In humans, binding to a 5000 lton protein is thought to reduce its enterohepatic culation (369).
ii. Lead. Lead is removed from the body at a slow rate.
hen lead was administered intravenously to s When administered to an animal, copper is rapidly
appear to be such appear to be such also to a mechanism that does not
appear to be suturable (405) . Copper can then be excreted
into bile (191, 888), stored in liver (89

of ouabain in bile (1216).
Biliary excretion of endogenous estrogens varies from decreases rapidly thereafter (167, 665); over 20% is ex-
20% to 60% depending upon the species (15). Although creted into the feces within th weight substances (194). In humans, binding to a 5000 dalton protein is thought to reduce its enterohepatic circulation (369).
 \ddot{u} . Lead. Lead is removed from the body at a slow rate.

When lead was administered int 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 excrete circulation (369).
 \vec{u} . 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 eliminate 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 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 in urine (112). When lead was similarly administered to 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 fece 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 a 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 in urine (167). The rate of excretion of lead into feces is highest during the first day after administration an decreases rapidly thereafter (167, 665); over 20% is excreted into the feces within the first 24-hours, 9% w highest during the first day after administration and
decreases rapidly thereafter (167, 665); over 20% is ex-
creted into the feces within the first 24-hours, 9% within
the second 24-hour period, with a rapid decline to m 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 excret the second 24-hour period, with a rapid decline to minie second 24-hour period, with a rapid decline to mini-
al amounts thereafter (665). Most of the lead excreted
to feces is via bile (112, 190). In humans, urine appears
be a more important route of elimination (596).
An ap

since they are glucuronidated before excretion they are tion gradient of 100 for lead is largely due to the gradient
probably secreted by the organic acid pathway.

e. METALS. Excretion of heavy metals into bile has the gr mal 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
in into feces is via bile (112, 190). In humans, urine app
to be a more important route of elimination (596).
An apparent transport maximum for excretion of
into bile (1.2 μ g/min/kg) suggests that lead may
actively transp to be a more important route of elimination (596).
An apparent transport maximum for excretion of lead
into bile $(1.2 \mu g/min/kg)$ suggests that lead may be
actively transported (665). The bile/plasma concentra-
tion gradient An apparent transport maximum for excretion of lead
into bile $(1.2 \mu g/min/kg)$ suggests that lead may be
actively transported (665). The bile/plasma concentra-
tion gradient of 100 for lead is largely due to the gradient
from t_{max} one (1.2 μ g/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 actively transported (665). The one/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 b

aspet

SEN AND
bound to proteins of varying molecular weights in bile im
(195). Liver proteins have the highest, plasma interme- of KLAASSE
(195). Liver proteins of varying molecular weights in
(195). Liver proteins have the highest, plasma interme-
diate, and bile the lowest affinity for lead. This sugge KLAASSEN AN
bound to proteins of varying molecular weights in bile
(195). Liver proteins have the highest, plasma interme-
diate, and bile the lowest affinity for lead. This suggests
that lead does not passively move from bound to proteins of varying molecular weights in bile im (195). Liver proteins have the highest, plasma interme-
diate, and bile the lowest affinity for lead. This suggests in that lead does not passively move from plasma (195). Liver proteins have the highest, plasma interme-
diate, and bile the lowest affinity for lead. This suggests
increase in its excretion into the bile (639). Mercury is
that lead does not passively move from plasma t (195). Liver proteins have the highest, plasma interme-
diate, and bile the lowest affinity for lead. This suggests in
that lead does not passively move from plasma to bile the
because of a higher affinity for bile than f (665). at lead does not passively move from plasma to bilcause of a higher affinity for bile than for plasma buther that excretion most likely is carrier mediate 55).
 iii. Manganese. In contrast to most other metals, man anese

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, man-
aganese is rapidly excreted from the body via th rather that excretion most likely is carrier mediated (665).
 iii. Manganese. In contrast to most other metals, man-

aganese is rapidly excreted from the body via the gas-

trointestinal tract with only trace amounts in (665). $\frac{1}{111}$ Manganese. In contrast to most other metals, manual aganese is rapidly excreted from the body via the gas-
goe trointestinal tract with only trace amounts in the urine. ind
Greenberg and colleagues (415 iii. Manganese. In contrast to most other metals, man-
aganese is rapidly excreted from the body via the gas-
trointestinal tract with only trace amounts in the urine.
Increenberg and colleagues $(415, 416)$ found that 9 aganese is rapidly excreted from the body via the gas-
trointestinal 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 trointestinal tract with only trace amounts in the urine. in
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 ad Greenberg and colleagues $(415, 416)$ found that 90% of a 1-mg dose injected intraperitoneally into rats was in the heces within 3 days. When mangnese was administered intravenously to rats, over 50% of the dose was in fe 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 sec moved by a single pass through the dose was in feces chemining the first 24 hours and 17% within the second 24-
hour period (634). About 40% of the manganese is re-
moved by a single pass through the liver which is a very within the first 24 hours and 17% within the second 24-
hour period (634) . About 40% of the manganese is re-
moved by a single pass through the liver which is a very
significant first-pass effect (1175) . Additional hour period (634). About 40% of the mandwed by a single pass through the liver
significant first-pass effect (1175). Addit
dicates the biliary excretion of manganese
on lysosomal uptake and release (1154).
There is an over by a single pass through the liver which is a very metaple. Therefore, the biliary excretion of manganese depends partly bill lysosomal uptake and release (1154). boothere is an overall bile/plasma concentration ratio exce

significant first-pass effect (1175). Additional work incomplicates the biliary excretion of manganese depends partly bile
on lysosomal uptake and release (1154). bout there is an overall bile/plasma concentration ratio e dicates the biliary excretion of manganese depends partly bile this on lysosomal uptake and release (1154). bound
There is an overall bile/plasma concentration ratio excrete
greater than 150 for manganese. Approximately t 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 There is an overall bile/plasma concentration ratio excreater than 150 for manganese. Approximately two 880) thirds of this overall gradient is due to the gradient from *vi* plasma to liver, and about one third from liver 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 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 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 Ci The large bile/plasma concentration ratio is difficult to
interpret because much of the manganese is not presen
as the free cation in bile (634, 1180). Tichy and Cikr
(1180) suggested that manganese may be transferrec
pass 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 non-
enzy as the free cation in bile (634, 1180). Tichy and Ciki
(1180) suggested that manganese may be transferre
passively from plasma to bile and then undergoes a nor
enzymatic complex formation in bile. Later studies ir
dicate t (1100) suggested that manganese may be transferred in
passively from plasma to bile and then undergoes a non-
ever, plasma and liver contain ligands with a higher to
affinity for manganese than bile (634). Thus it would hi enzymatic complex formation in bile. Later studies in-
dicate the metal is bound to bile pigments (1181). How-
ever, plasma and liver contain ligands with a higher to
affinity for manganese than bile (634). Thus it would dicate the metal is bound to bile pigments (1181). How-
ever, plasma and liver contain ligands with a higher to
affinity for manganese than bile (634). Thus it would higher
appear that manganese is not transferred from pla ever, 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. A affinity for manganese than b
appear that manganese is not
to bile by a passive mechanism
one. About 35% of excreted n
terohepatic circulation (191).
iv. Arsenic. Arsenic is slowly pear that manganese is not transferred from plasma (17
bile by a passive mechanism, but rather by an active the
e. About 35% of excreted manganese undergoes en-
kg
ohepatic circulation (191).
iv. Arsenic. Arsenic is slowly

to bile by a passive mechanism, but rather by an active
one. About 35% of excreted manganese undergoes en-
terohepatic circulation (191).
 \dot{w} . Arsenic. Arsenic is slowly eliminated from the body
as are most metals. Wh one. About 35% of excreted manganese undergoes en-
terohepatic circulation (191). can
iv. Arsenic. Arsenic is slowly eliminated from the body
gel
as are most metals. When arsenic trichloride was ad-
in minstered intravenou terohepatic circulation (191).
 iv. Arsenic. Arsenic is slowly eliminated from the body

as are most metals. When arsenic trichloride was ad-

minstered intravenously to rats, 13% was excreted the

first day and only an iv. Arsenic. Arsenic is slowly eliminated from the body gel as are most metals. When arsenic trichloride was ad-
minstered intravenously to rats, 13% was excreted the but
first day and only an additional 7% in the next 6 as are most metals. When arsenic trichloride was ad-
minstered 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
ur minstered intravenously to rats, 13% was excreted the bufirst day and only an additional 7% in the next 6 days. pe Of that excreted in the first day, 60% was eliminated in urine and 40% in feces (633) . The conc first day and only an additional 7% in the next 6 days. pet Of that excreted in the first day, 60% was eliminated in urine and 40% in feces (633). The concentration of is are are are are are are are to bile are the 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 b urine and 40% in feces (633). The concentration of is for arsenic is 600-times higher in bile than plasma. The The gradients from plasma to liver and from liver to bile are the greater than one, the latter usually being th arsenic is 600-times higher in bile than plasma. The The gradients from plasma to liver and from liver to bile are the greater than one, the latter usually being the larger ratio.
This high concentration of arsenic in bile gradients from plasma to liver and from liver to bile are the greater than one, the latter usually being the larger ratio. This high concentration of arsenic in bile is not due to a its or higher affinity of arsenic for ma 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 bile
in liver because macromolecules in bi 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 (6 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 in liver because macromolecules in bile have affinity for arsenic whereas the liver does (633) bile/plasma concentration ratio suggests that excreted into bile by an active transport system mo transport maximum has been *v. Mercury.* The fecal route appears that arsenic creted into bile by an active transport system, althout ransport maximum has been demonstrated.
v. Mercury. The fecal route appears to be more import than the urinary ro

one) plasma concentration ratio suggests that arsent is
excreted into bile by an active transport system, although violation to transport maximum has been demonstrated.
v. Mercury. The fecal route appears to be more impor-

D WATKINS
imum for inorganic mercury appears to exist; as the dose
of mercuric chloride is increased there is a proportional D WATKINS
imum for inorganic mercury appears to exist; as the doss
of mercuric chloride is increased there is a proportiona
increase in its excretion into the bile (639). Mercury i D WATKINS
imum 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 revie imum 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 imum 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 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 con-
sidered a class B compound. Concentration of mer find the first metal discussed in this review that is not cosidered a class B compound. Concentration of mercury is bound to large molec-
in liver is slightly higher and that in bile is about of fourth that in plasma. Merc 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 molec in liver is slightly higher and that in bile is about one-
fourth that in plasma. Mercury is bound to large molec-
ular weight proteins in bile (471) and about 20% under-
goes enterohepatic circulation (191). Recent eviden fourth that in plasma. Mercury is bound to large molec-
ular weight proteins in bile (471) and about 20% under-
goes enterohepatic circulation (191). Recent evidence
indicates mercury is excreted into bile with GSH but as
 ular weight proteins in bile (471) and abgoes enterohepatic circulation (191). Indicates mercury is excreted into bile was GSH auto-oxidizes to GSSG, the metal higher molecular weight proteins (63). The biliary excretion o es enterohepatic circulation (191). Recent evidence
dicates mercury is excreted into bile with GSH but as
SH auto-oxidizes to GSSG, the metal associates with
gher molecular weight proteins (63).
The biliary excretion of me

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 dos 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 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 t 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
methylmer concentration ratio after methylmercury chloride is
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 o 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 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 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 excrete 880). **is than in liver (639). Most of the mercury in bile is**

und to proteins and amino acids (857) after it is

creted as methylmercury glutathione (62, 485, 858,

0).
 vi. Cadmium. The major route of excretion of cadmium

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 excre apparently as inethymetrury glutatione (02, 460, 666, 688).
 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 exc 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 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
l 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 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 cadand 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 cad-
mium 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 cad-
mium excreted into bile is related to dose but opposit This is most likely due to saturation of cadmium binding
to metallothionein at higher doses. The percent of cad-
mium excreted into bile is related to dose but opposite
to that observed for most chemicals secreted into bil to metallothionein at higher doses. The percent of cad-
mium 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 mium 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 increase 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 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 o (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. Sep 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 kg and 130 at 3.0 mg/kg (659). The concentration of cadmium in bile is actually lower than in liver. Sephades gel chromatography studies demonstrate that cadmium in bile is not bound to large macromolecules (471, 676) but 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,
perh I chromatography studies demonstrate that cadmium
bile is not bound to large macromolecules (471, 676)
t is excreted as a low molecular weight compound,
rhaps complexed with glutathione (180).
vii. Other Metals. The majo

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 littl 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). perhaps complexed with glutathione (180)
uii. Other Metals. The major route of ex-
is fecal with little being excreted into urin
The main pathway is not via bile but appear
the intestinal wall (680, 802, 810, 1201).
The wii. Other Metals. The major route of excretion for zinc
fecal with little being excreted into urine (1082, 1122).
ne main pathway is not via bile but appears to be across
e intestinal wall (680, 802, 810, 1201).
The impo

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 I he main pathway is not via one out 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 importance of the oxidation
its excretion has been demonstrated
bile is not the major route for excretin, it has been shown that divalent
bile while quadravalent tin is not.
About 70% of silver is excreted 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% o

bile is not the major route for excretion of any form
tin, it has been shown that divalent tin is excreted in
bile while quadravalent tin is not.
About 70% of silver is excreted into bile and 1%
urine within 4 days 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 concen-
tration in bile is 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 concen-

tration in bile is about 20 times higher than in plasma.

Concentration gr About 70% of silver is excreted into bile and 1% in
urine within 4 days of administration (652). Its concen-
tration in bile is about 20 times higher than in plasma.
Concentration gradient for silver from plasma to liver i urine within 4 days of ad
tration in bile is about 20
Concentration gradient fo
about equal to that from
maximum is demonstrabl

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PHARMACOLOGICAL REVIEWS

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BILE FORMATION, HEPATIC I
Beryllium is also excreted into bile, but urine appear
to be important (192). Cobalt is also preferentially elim-
inated via the urine, but the fraction excreted into bil BILE FORMATION, HEPATIC UPTAKI
Beryllium is also excreted into bile, but urine appears more
to be important (192). Cobalt is also preferentially elim-
increases with dose (198).
exc Beryllium is also excreted into bile, but urine appears moto be important (192). Cobalt is also preferentially elim-

inated via the urine, but the fraction excreted into bile motoreases with dose (198).
 viii. Role of Gl

inated via the urine, but the fraction excreted into bile
increases with dose (198).
viii. Role of Glutathione in Metal Excretion. Methyl-
mercury, copper, silver, and zinc are excreted into bile
via a proposed mechanism w increases with dose (198). excret

viii. Role of Glutathione in Metal Excretion. Methyl-

molecule (26-28, 880, 963). High concentrations of GSH

molecule (26-28, 880, 963). High concentrations of GSH

molecule (26-28, 880 *uiii. Role of Glutathione in Metal Excretion.* Methyl-
mercury, copper, silver, and zinc are excreted into bile
via a proposed mechanism where GSH is the carrier Exc
molecule (26–28, 880, 963). High concentrations of GSH mercury, copper, silver, and zinc are excreted into bi
via a proposed mechanism where GSH is the carri
molecule (26–28, 880, 963). High concentrations of GS
are found in rat bile (1 to 3 mM) and the metal-GS
stability con via a proposed mechanism where GSH is the carrier Ex
molecule (26–28, 880, 963). High concentrations of GSH more
are found in rat bile (1 to 3 mM) and the metal-GSH the
stability constants are very high (silver, K=10¹⁵; molecule (26–28, 880, 963). High concentrations of GSH are found in rat bile (1 to 3 mM) and the metal-GSH that stability constants are very high (silver, K=10¹⁵; meth-
stability constants are very high (silver, K=10¹⁵ are found in rat bile (1 to 3 mM) and the metal-GSH
stability constants are very high (silver, $K=10^{15}$; meth-
ylmercury, $K=10^{15.9}$). Infusion of GSH enhances the
biliary excretion of methylmercury (763). Gel filtrat stability constants are very high (silver, $K=10^{15}$; me
ylmercury, $K=10^{15.9}$). Infusion of GSH enhances i
biliary excretion of methylmercury (763). Gel filtrati
studies suggest that the silver ion in bile is predomin ylmercury, K=10^{15.9}). Infusion of GSH enhances
biliary excretion of methylmercury (763). Gel filtra
studies suggest that the silver ion in bile is predomina
found in a 1:1 complex with GSH and in some poly
clear complexe 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 polynu-
clear complexes with GSH or biliary proteins. Pretre studies suggest that the silver ion in bile is predominantly nound in a 1:1 complex with GSH and in some polynu-
clear complexes with GSH or biliary proteins. Pretreat-
ment of rats with either diethyl maleate or selenite, found in a 1:1 complex with GSH and in some polynu-
clear complexes with GSH or biliary proteins. Pretreat-
ment of rats with either diethyl maleate or selenite, pat
depleters of GSH (511, 967), inhibits the biliary excret clear 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), a ment of rats with either diethyl maleate or selenite, podepleters of GSH (511, 967), inhibits the biliary excretion also f copper (26), silver (27), methylmercury (29, 30), and usinc (28). Administration of BSP or indocyan depleters of GSH (511, 967), inhibits the biliary excretion also for copper (26), silver (27), methylmercury (29, 30), and uzinc (28). Administration of BSP or indocyanine green, awhich bind to ligandin, decreases the bili of copper (26), silver (27), methylmercury (29, 30), a
zinc (28). Administration of BSP or indocyanine gree
which bind to ligandin, decreases the biliary excretion
methylmercury while bilirubin has no effect (764). The
dat zinc (28). Administration of BSP or indocya
which bind to ligandin, decreases the biliary excretive methylmercury while bilirubin has no effect (
data suggest that glutathione conjugation matant in the biliary excretion of methylmercury while bilirubin has no effect (764). These
data suggest that glutathione conjugation may be impor-
tant in the biliary excretion of some metals.
VII. Factors Influencing Hepatobiliary

Transport

A. Physicochemical Characteristics of some metals.
 A. Physicochemical Characteristics of Chemicals
 A. Physicochemical Characteristics of Chemicals
 Excreted into Bile **Factors In VII. Factors In A. Physicochemical Christian Property Control Christian Property and Mole**
L Polarity and Mole

1. **1. Physicochemical Characteristics of Chemicals**
1. *Polarity and Molecular Size*. Two physicochemic
1. *Polarity and Molecular Size*. Two physicochemic
1. *Polarity and molecular weight, can influence tl* A. Physicochemical Characteristics of Chemicals

Foreverting the section of a compound (1107). Presence of a

factors, polarity and molecular weight, can influence the diffusion of a compound (1107). Presence of a Excreted into Bile

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 For

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 moi 1. Polarity and Molecular Size. Two physicochemical or factors, polarity and molecular weight, can influence the diffulity excretion of a compound (1107). Presence of a on strongly polar group or potentially ionizable moi 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 grou 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 biotra 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 bio-
transformation. Conjugations with glucuronic acid, sulf molecule augments biliary excretion. This polar group
may be part of the parent molecule or acquired by bio-
transformation. Conjugations with glucuronic acid, sul-
fate, glutathione, glycine, and taurine are particularly
 may be part of the parent molecule or acquired by bio-
transformation. Conjugations with glucuronic acid, sul-
fate, glutathione, glycine, and taurine are particularly
significant in adding polar groups. Such moieties all transformation. Conjugations with glucuronic acid, sufate, glutathione, glycine, and taurine are particular significant in adding polar groups. Such moieties allow molecule to exist at physiological pH as a water solub ani fate, glutathione, glycine, and taurine are particularly rat livers remove taurocholate (357) and rose bengal
significant in adding polar groups. Such moieties allow a (358) substantially faster than can be accounted for b anion. There is no charged center on the cardiac glyco-
sides and no apparent correlation between polarity of the
glycosides and biliary excretion in rats, dogs, rabbits
(1016), or guinea pigs (777). However, presence of o molecule to exist at physiological pH as a water soluble
anion. There is no charged center on the cardiac glyco-
sides and no apparent correlation between polarity of the
glycosides and biliary excretion in rats, dogs, rab 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 the (1016), or guinea pigs (777). However, presence o sides 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 f glycosides and biliary excretion in rats, dogs, rabbits the ext (1016), or guinea pigs (777). However, presence of one or dicted in
more water-soluble sugar residues can compensate for appear.
the lack of a charged moiety (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 for more water-soluble sugar residues can compensate
the lack of a charged moiety and facilitate excreti
Many drugs excreted into bile are eliminated in the for
of metabolites. In essence, biotransformation (note
conjugation) 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 introduc creasing the compound's molecular weight (1107). metabolites. In essence, biotransformation (notably miguation) augments the biliary excretion by introduc-
Brauer as a strong polar center into the molecule and by in-
Reasing the compound's molecular weight (1107).
Braue

conjugation) augments the biliary excretion by introduc-
ing a strong polar center into the molecule and by in-
creasing the compound's molecular weight (1107).
Brauer (135) noted that substances which are highly
concentr ing 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 creasing the compound's molecular weight (1107).
Brauer (135) noted that substances which are highly ics
concentrated in bile are usually organic carboxylic acids am
with molecular weights greater than 300. Sperber (1115) 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
re concentrated in bile are usually organic carboxylic according weights greater than 300. Sperber (11 stated that the compounds efficiently secreted by renal tubules have low molecular weights (200 to 40 whereas chemicals ex with molecular weights greater than 300. Sperber (1115) extrapolate results obtained in laboratory animals to stated that the compounds efficiently secreted by the predict effects in humans. Species have been classified r

BILE FORMATION, HEPATIC UPTAKE, AND BILIARY EXCRETION 33
Beryllium is also excreted into bile, but urine appears monocyclic benzene derivatives (8), bi- and triphenyls
to be important (192). Cobalt is also preferentially e AKE, AND BILIARY EXCRETION 33
monocyclic benzene derivatives (8), bi- and triphenyls (1808) KE, AND BILIARY EXCRETION 33

(1808), and sulfonamides (809) indicate compounds whose

(1808), and sulfonamides (809) indicate compounds whose

molecular weights exceed a threshold of 325 ± 50 are EXECTION 33
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 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. Thre 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. Thre (808), and sulfonamides (809) indicate compounds whos
molecular weights exceed a threshold of 325 ± 50 are
excreted in appreciable quantities into bile. Threshole
molecular weights for biliary excretion in the guinea pi 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 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 w 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 thes rabbit, and man are 400, 475, and 500, respectivel
Excretion occurs mainly via the bile for xenobiotics wire
molecular weights greater than 850 (487). Above the
thresholds, no relationship exists between the extent
biliary 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). Co molecular weights greater than 850 (487). Above these
thresholds, no relationship exists between the extent of
biliary excretion and molecular weight (488, 489). Com-
parison of the excretion of monoquaternary ammonium
cat thresholds, no relationship exists between the extent of
biliary excretion and molecular weight (488, 489). Com-
parison of the excretion of monoquaternary ammonium
cations in bile by rat, rabbit, and guinea pig indicate t 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 rison of the excretion of monoquaternary ammonium
tions in bile by rat, rabbit, and guinea pig indicate that
blecular weight may not be important in organic cation
cretion (516).
2. Plasma Protein Binding. Solutes destined

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 he-
patic metabolism and/or excretion c molecular weight may not be important in organic cation
excretion (516).
2. Plasma Protein Binding. Solutes destined for he-
patic metabolism and/or excretion commonly bind to
albumin in the circulation and hence, have sma excretion (516).

2. Plasma Protein Binding. Solutes destined for he-

patic metabolism and/or excretion commonly bind to

albumin in the circulation and hence, have smaller vol-

umes of distribution. Familiar examples in 2. Plasma Protein Binding. Solutes destined for he-
patic metabolism and/or excretion commonly bind to
albumin in the circulation and hence, have smaller vol-
umes of distribution. Familiar examples include bile
acids, bil patic metabolism and/or excretion commonly bind to
albumin in the circulation and hence, have smaller vol-
umes of distribution. Familiar examples include bile
acids, bilirubin, sulfobromophthalein, indocyanine green,
and 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 chemic umes 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 impor-
tant acids, bilirubin, sulfobromophthalein, indocyanine green,
and many drugs. Although important in transporting
chemicals to the liver, albumin does not play an impor-
tant role in hepatic extraction or biliary elimination (4 and many drugs. Although important in transporting
chemicals to the liver, albumin does not play an impor-
tant role in hepatic extraction or biliary elimination (400,
794, 1038, 1281, 1282). Most chemicals excreted into b 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 sol tant role in hepatic extraction or biliary elimination (40
794, 1038, 1281, 1282). Most chemicals excreted into bi
are highly bound to plasma proteins. How free solu
becomes available to the cell surface, however, is n
cle 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 dissoare highly bound to plasma proteins. How free solut
becomes available to the cell surface, however, is no
clear. The conventional view is that spontaneous disso
ciation of the albumin-ligand complex allows the liver to
rem becomes available to the cell surface, however, is not clear. The conventional view is that spontaneous disso-
ciation of the albumin-ligand complex allows the liver to
remove much more solute than is free in the circulati clear. The conventional view is that spontaneous disso-
ciation 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 ciation 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 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 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 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. ly mechanism. For example, less than 1% of serum
irubin is free in the peripheral circulation, but its
patic extraction is at least an order of magnitude
gher.
Forker and colleagues recently reported that perfused
t livers

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 beng 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 b 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 ben perfusate. Both studies demonstrate that increasing the
perfusate. Both studies demonstrate that increasing the
perfusate. Both studies demonstrate that increasing the
perfusate albumin concentration leads to a reduction i perfusate albumin concentration leads to a reduction in 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 perfusate albumin concentration leads to a reduction in
the extraction fraction that is much less than that pre-
dicted by equilibrium binding measured in vitro. Thus it
appears that liver cells enjoy a special mechanism f the extraction fraction that is much less than that
dicted by equilibrium binding measured in vitro. Tl
appears that liver cells enjoy a special mechanism
enhancing the dissociation of ligands from albumin
that the release dicted by equinorially binding measured in virto. 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.

Xenobiotics

1. **1.** The release mechanism has a limited capacity.

1. *Biological Factors Influencing Biliary Excretion of*

1. *Species Variation*. The amount of an organic chem-

1. *Species Variation*. The amount of an organic chem Interact the second in the metal that is extended that is excretion of
 I. Species Variation. The amount of an organic chem-

ical or a metal that is excreted in bile varies widely

among species. These differences make B. Biological Factors Influencing Biliary Excretion of
Xenobiotics
1. Species Variation. The amount of an organic chem-
ical or a metal that is excreted in bile varies widely
among species. These differences make it diffic Xenobiotics
1. Species Variation. The amount of an organic chem-
ical or a metal that is excreted in bile varies widely
among species. These differences make it difficult to
extrapolate results obtained in laboratory anima 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 ical 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
int 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 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)

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Excretors; the rabbit, guinea pig, and rhesus monkey are rate relatively poor; and cat and sheep are intermediate. Un-REAASSEN
excretors; the rabbit, guinea pig, and rhesus monkey are
relatively poor; and cat and sheep are intermediate. Un-
fortunately, the significance of these classifications is KLAASSEN AND
excretors; the rabbit, guinea pig, and rhesus monkey are rate
relatively poor; and cat and sheep are intermediate. Un-
fortunately, the significance of these classifications is are
reduced by a large number of 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 relatively poor; and cat and sheep are intermediate. Un-
fortunately, the significance of these classifications is arsenic, manganese) appears to be due to differences in
reduced by a large number of exceptions. For exampl relatively poor; and cat and sheep are intermediate. Un-
fortunately, the significance of these classifications is arse
reduced by a large number of exceptions. For example, mov
rats excrete about 50% of an injected dose o fortunately, the significance of these classifications is are
reduced by a large number of exceptions. For example, means excrete about 50% of an injected dose of ouabain from
into bile in 2 hours whereas only 0.5% is exc 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 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 ex-
cre dogs in that time (1016). Chromoglycate is excreted as times the rate in rats (659), whereas silver is excreted
well by the monkey as the rat (45). Terbutaline is ex-
0.1 to 0.01 times the rate in rats for rabbits and dog dogs in that time (1016). Chromoglycate is excreted as time
well by the monkey as the rat (45). Terbutaline is ex-
creted extensively in rats (40% of injected dose) but not
resp
in dogs or man (1% to 2% of dose) (852). Co 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
fou creted 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 specie in dogs or man $(1\%$ to 2% of dose) (852) . Comparison of set the excretion of phenol red and indocyanine green in the four marine species indicates several species variations (649) . Indocyanine green was excreted 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
 four marine species indicates several species variation (949). Indocyanine green was excreted unchanged by alfour fish whereas phenol red was eliminated into bile a the glucuronide by dogfish shark and skates and unchanged (949). Indocyanine green was excreted unchanged by all mat
four fish whereas phenol red was eliminated into bile as acid
the glucuronide by dogfish shark and skates and un-
slight changed by hagfish and flounder. A recent four fish whereas phenol red was eliminated into bile as
the glucuronide by dogfish shark and skates and un-
changed by hagfish and flounder. A recent study com-
pared the biliary excretion of eight cholephilic anions by
a the glucuronide by dogfish shark and skates and un-
changed by hagfish and flounder. A recent study com-
pared the biliary excretion of eight cholephilic anions by
actimice and rats (428). Male Swiss-Webster mice excreted changed 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 pared 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. mice and rats (428). Male Swiss-Webster mice excreted the indocyanine green, rose bengal, DBSP, and eosine at a grate 120% to 460% higher than male Sprague-Dawley D
rats. Secretion of bromcresol green and BSP-GSH contigrat indocyanine green, rose bengal, DBSP, and eosine a
rate 120% to 460% higher than male Sprague-Daw
rats. Secretion of bromcresol green and BSP-GSH co
jugate were similar in the two species, whereas that
amaranth was lower i rate 120% to 460% higher than male Sprague-Dawley Die
rats. Secretion of bromcresol green and BSP-GSH con-
jugate were similar in the two species, whereas that of inte
amaranth was lower in mice. Depression of bile producrats. Secretion of bromcresol green and BSP-GSH con-
jugate were similar in the two species, whereas that of
amaranth was lower in mice. Depression of bile produc-
tion by cholestatic organic anions was stronger, and
stimu jugate were similar in the two species, whereas that of inter-
amaranth was lower in mice. Depression of bile production
tion by cholestatic organic anions was stronger, and exc
stimulation of bile flow by choleretic acid amaranth was lower in mice. Depression of bile production by cholestatic organic anions was stronger, and excretial stimulation of bile flow by choleretic acids was weaker of dietin mice than in rats. Differences in bilia tion 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 μ mol/min/kg), bile f 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 μ mol/min/kg), bile flow
rate (mouse, 102; rat, 69 μ l/min/kg), and live in mice than in rats. Differences in biliary bile acid excretion (mouse, 3.62; rat, 1.42 μ mol/min/kg), bile flow rate (mouse, 102; rat, 69 μ l/min/kg), and liver weight (mouse, 57; rat, 38 g/kg) but not hepatic ligan excretion (mouse, 3.62; rat, 1.42 μ mol/min/kg), bile flow 6
rate (mouse, 102; rat, 69 μ l/min/kg), and liver weight b
(mouse, 57; rat, 38 g/kg) but not hepatic ligandin con-
centration (mouse, 132; rat, 214 nmol BSP/ rate (mouse, 102; rat, 69 μ l/min/kg), and liver weigl (mouse, 57; rat, 38 g /kg) but not hepatic ligandin concentration (mouse, 132; rat, 214 nmol BSP/g of live may explain the differences in organic anion excretic in centration (mouse, 132; rat, 214 nmol BSP/g of liver) the may explain the differences in organic anion excretion bili
into bile between mice and rats. Until the biliary secrebef
tion of cationic and neutral organic compou 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 c 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 c d, the mouse can only be tentatively classified as a good
liary excretor. In general, rats and mice may be consid-
ed to excrete chemicals into bile better than other
ecies.
There is a paucity of data examining biliary exc biliary excretor. In general, rats and mice may be considered to excrete chemicals into bile better than othe species.
There is a paucity of data examining biliary excretion
in humans due to difficulties in obtaining sampl

everal to excrete chemicals into bile better than other are species.

There is a paucity of data examining biliary excretion 65

in humans due to difficulties in obtaining samples. How-

in ever, several xenobiotics have b species. dow
There is a paucity of data examining biliary excretion 658
in humans due to difficulties in obtaining samples. How-
in
ever, several xenobiotics have been detected in human Ta
bile and have been compiled (657, There is a paucity of data examining biliary excretion 6
in humans due to difficulties in obtaining samples. How-
ever, several xenobiotics have been detected in human 7
bile and have been compiled (657, 999). Commonly use in humans due to difficulties in obtaining samples. How-
ever, several xenobiotics have been detected in human
bile and have been compiled (657, 999). Commonly used
drugs concentrated or readily excreted in bile include
me ever, 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
a 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 digi-
 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 digi-
 meperidine (278), ampicillin (144), several cephalosporin of analogs (143, 959), erythromycin (174), clindamycin (66
(145), practolol and acibutalol (594), digoxin and digitoxin (672, 1025), adriamycin (987), vincristine ((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 (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 toxin (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, pro indocyanine green and iogly
psychotropic agents diazepai
1170). Conjugates of several
progesterone, corticosterone,
creted into bile (698, 1107).
There are also species diffe There are also species differences in the rate of biliary
There are also species differences in the rate of biliary
There are also species differences in the rate of biliary
Innsport. BSP is readily excreted by rat, rabbi

creted 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 progesterone, corticosterone, and cortisone are also ex-
creted into bile (698, 1107). There are also species differences in the rate of biliary live
transport. BSP is readily excreted by rat, rabbit, dog, between and man creted into bile (698, 1107).

There are also species differences in the rate of biliary litransport. BSP is readily excreted by rat, rabbit, dog, b

and man but the T_m for BSP is 5 to 10 times higher in a

rats and rab There are also species differences in the rate of biliary
transport. BSP is readily excreted by rat, rabbit, dog, betwee
and man but the T_m for BSP is 5 to 10 times higher in appear
rats and rabbits than in dogs or man

KLAASSEN AND WATKINS
monkey are rate since biliary BSP concentrations are comparable. D WATKINS
Tate since biliary BSP concentrations are comparable.
Species variation in the biliary excretion of metals (lead,
arsenic, manganese) appears to be due to differences in D WATKINS
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 bi 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 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 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 ca 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 cad-
mium by rabbits is about 0.16 and that of dogs 0.003
time movement of metal from hepatocytes into bile and not
from plasma into liver (644). Biliary excretion of cad-
mium by rabbits is about 0.16 and that of dogs 0.003
times the rate in rats (659), whereas silver is excreted
0.1 from plasma into liver (644) . Biliary excretion of cad-
mium 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 times the rate in rats (659), whereas silver is excreted 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, ar-
senic, manganese, and methylmercury to a greater ext 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 biotransfo 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 biotransfo senic, manganese, and methylmercury to a greater extent
than rabbits and both species had higher rates than dogs
(633, 634, 639, 665). Species differences in biotransfor-
mation may also influence biliary excretion. Ethacr 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 o (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 $($ mation 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 o 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 (17 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 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 th 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 th 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 e 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 hyd 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 bili 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 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, to the monosulfate before glucuronidation and biliary
excretion. In guinea pigs, however, appreciable amounts
of diethylstilbestrol monosulfate are either sulfated, glu-
curonidated, or unchanged before excretion into bile excretion. In guinea pigs, however, appreciable amounts
of diethylstilbestrol monosulfate are either sulfated, glu-
curonidated, or unchanged before excretion into bile (66,
67). Finally, species differences in hepatic blo of diethylstilbestrol monosulfate are either sulfated, glu-
curonidated, or unchanged before excretion into bile (66,
67). Finally, species differences in hepatic blood flow and
bile flow do not appear to correlate with bi curonidated, 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 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 vari 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 nece 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
dif excretion. **2. Sex.** Differences in the complete understanding of species differences in the complex process involved in biliary excretion.

2. Sex. Differences in biliary excretion between male slightly choleretic (1078) or even cholestatic (311) in rabbits. Since the increased bile flow is due to the osmotic rativity of the glutathione conjugate in bile (178, 658), this species difference may be accounted for b

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 (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 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 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).
T 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. It 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. Howeve in rats for indocyanine green and chlorothiazide (466).
Tartrazine (100) is secreted metabolically unchanged. Its
excretion is more efficient in female rats. However, an-
other study found no difference in the biliary excr (667). other 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

other 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
 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 μ M dinitrotoluene, male Fischer 344 rats ex (667).

A recent study indicates a sex difference in biliary

excretion of 2,4-dinitrotoluene (120). After perfusion

with 20 μ M dinitrotoluene, male Fischer 344 rats ex-

creted more 2,4-dinitrobenzyl alcohol glucuron A recent study indicates a sex difference in biliary
excretion of 2,4-dinitrotoluene (120). After perfusion
with 20 μ M dinitrotoluene, male Fischer 344 rats ex-
creted more 2,4-dinitrobenzyl alcohol glucuronide into
bi excretion of 2,4-dinitrotoluene (120). After perfusion with 20 μ M dinitrotoluene, male Fischer 344 rats excreted more 2,4-dinitrobenzyl alcohol glucuronide intitial (392 nmol) than female rats (172 nmol). Capacition me with 20 μ M 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 mac-
r creted 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 mac-
romolecular covalent binding were not different between
 bile (392 nmol) than female rats (172 nmol). Capac
for metabolism of 2,4-dinitrophenol and for hepatic me
romolecular covalent binding were not different betwe
livers from male and female rats. The major differen
between t for metabolism of 2,4-dinitrophenol and for hepatic mac-
romolecular covalent binding were not different between
livers from male and female rats. The major difference
between the sexes in the disposition of 2,4-dinitrophe 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

BILE FORMATION, HEPATIC UP
 μ l/min/kg) than normal female or male rats (50 μ l/min/
kg), and both bile acid-dependent and independent frac-BILE FORMATION, HEPATIC U
 μ /min/kg) than normal female or male rats (50 μ /min/

kg), and both bile acid-dependent and independent frac-

tions of canalicular bile flow are increased (667). The BILE FORMATION, HEPATIC UPTAK μ l/min/kg) than normal female or male rats (50 μ l/min/ and kg), and both bile acid-dependent and independent fractions of canalicular bile flow are increased (667). The calcatating rats μ l/min/kg) than normal female or male rats $(50 \ \mu$ l/min/ and kg), and both bile acid-dependent and independent frac-
tions of canalicular bile flow are increased (667). The can
lactating rats tend to excrete indocyani μ l/min/kg) than normal female or male rats (50 μ l/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 kg), and both bile acid-dependent and independent fra
tions of canalicular bile flow are increased (667). Tl
lactating rats tend to excrete indocyanine green to
greater extent than normal rats, but no significant di
ferenc tions of canalicular bile flow are increased (667).
lactating rats tend to excrete indocyanine green
greater extent than normal rats, but no significant
ferences in biliary excretion of DBSP, ouabain or a
anth were observe restating rats tend to excrete indocyanine green to a witubeted vertex extent than normal rats, but no significant dif-

rences in biliary excretion of DBSP, ouabain or amar-

th were observed in male and female rats (667)

greater extent than normal rats, but no significant deferences in biliary excretion of DBSP, ouabain or amanth were observed in male and female rats (667).
3. Age. The effects of aging on drug disposition m
result from pro ferences in biliary excretion of DBSP, ouabain or amar-
anth were observed in male and female rats (667).
3. Age. The effects of aging on drug disposition may
result from progressive physiological changes in metab-
olism, anth were observed in male and female rats (667).

3. Age. The effects of aging on drug disposition may

result from progressive physiological changes in metab-

olism, excretion, tissue distribution, and blood flow (609,
 3. Age. The effects of aging on drug disposition may
result from progressive physiological changes in metab-
olism, excretion, tissue distribution, and blood flow (609,
610, 1200). The plasma clearance of several drugs tha result from progressive physiological changes in metab-
olism, excretion, tissue distribution, and blood flow (609, wh
610, 1200). The plasma clearance of several drugs that rat
require hepatic metabolism is depressed in a olism, 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 610, 1200). The plasma clearance of several drugs that rat
require hepatic metabolism is depressed in aged animals bend
and corresponds with decreased activity of hepatic drug
metabolizing systems (659). The terminal dispo 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
 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 ha etabolizing systems (659). The terminal disposition loss of benzodiazepines in plasma is slightly longer in is
riatric patients and depends on volume of distribution h
17, 760, 1069).
Decreased biliary excretion of BSP has

phase of benzodiazepines in plasma is slightly longer in is
geriatric patients and depends on volume of distribution her
(517, 760, 1069).
Decreased biliary excretion of BSP has been observed Si
in older rats (609). Kitani geriatric patients and depends on volume of distributio
(517, 760, 1069).
Decreased biliary excretion of BSP has been observe
in older rats (609). Kitani et al. (614) noted a mark
difference in the plasma disappearance and tion of BSP has been observed

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 excre-

toon of ouabain betwe Decreased biliary excretion of BSP has been observed Sir
in older rats (609). Kitani et al. (614) noted a marked tole
difference in the plasma disappearance and biliary excre-
tion of ouabain between young and older rats. in older rats (609). Kitani et al. (614) noted a marked to difference in the plasma disappearance and biliary excretion of ouabain between young and older rats. They suggested that differences in bile production may be se difference in the plasma disappearance and biliary excretion of ouabain between young and older rats. They suggested that differences in bile production may be seemportant for the age-related effects. A recent study has of tion 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-
monthsuggested that differences in bile production may
important for the age-related effects. A recent study h
examined the pharmacokinetics of ouabain in 2- and
month-old rats (527). Plasma ouabain concentratio
were significan important for the age-related effects. A recent study has of lexamined the pharmacokinetics of ouabain in 2- and 6-
month-old rats (527). Plasma ouabain concentrations mu
were significantly higher in the older rats due to examined the pharmacokinetics of oua
month-old rats (527). Plasma ouabais
were significantly higher in the older ration in the apparent volume of distrit
decrease in the biliary excretory rate.
BSP retention in plasma incr onth-old rats (527). Plasma ouabain concentrations multive significantly higher in the older rats due to a reduc-
born in the apparent volume of distribution and not a (522
crease in the biliary excretory rate.
BSP retenti

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 ye tion in the apparent volume of distribution and not a (522
decrease in the biliary excretory rate. green BSP retention in plasma increases significantly in (525
humans around 40 years of age (609). Similar results H
were o decrease in the biliary excretory rate.
BSP retention in plasma increases significantly in
humans around 40 years of age (609). Similar result
were observed with indocyanine green clearance in
healthy geriatric Japanese me BSP retention in plasma increases significantly in (523
humans around 40 years of age (609). Similar results H
were observed with indocyanine green clearance in to the
healthy geriatric Japanese men (609). Furthermore, stu humans around 40 years of age (609). Similar results Hepatic uptake of taurocholate in fetal sheep is similar
were observed with indocyanine green clearance in to that in adults. However, adult liver excretes the tracer
he were observed with indocyanine green clearance in to
healthy geriatric Japanese men (609). Furthermore, stud-
ies of antipyrine and indocyanine green clearance in in
geriatric patients indicate impairment depends not only
 healthy geriatric Japanese men (609). Furthermore, studies of antipyrine and indocyanine green clearance is geriatric patients indicate impairment depends not on on the effects of aging on hepatic blood flow and activite o ies of antipyrine and indocyan
geriatric patients indicate impair
on the effects of aging on hepatic
of drug metabolizing enzymes but
factors such as smoking (1283).
More extensive work has eval riatric patients indicate impairment depends not only
the effects of aging on hepatic blood flow and activity
drug metabolizing enzymes but also on environmenta
tors such as smoking (1283).
More extensive work has evaluate

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 funct 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 physi factors such as smoking (1283).
More extensive work has evaluated the developme
of hepatic excretory function. Newborn animals are r
miniature adults, either physiologically or in their
sponse to xenobiotics (259, 761, 108 More extensive work has evaluated the development 2 of hepatic excretory function. Newborn animals are not timinature adults, either physiologically or in their response to xenobiotics ($259, 761, 1085$). Possible mecha of hepatic excretory function. Newborn animals are n
miniature adults, either physiologically or in their r
sponse to xenobiotics (259, 761, 1085). Possible mech
nisms that may account for differences in sensitivi
between miniature adults, either physiologically or in their re-
sponse to xenobiotics (259, 761, 1085). Possible mecha-
nisms that may account for differences in sensitivity la
between mature and immature animals include varia-
(between mature and immature animals include varia-
tions in absorption, distribution, biotransformation, ex-
cretion, and sensitivity of affected tissues. Biliary excre-
tion is not mature in newborn rats (626), dogs and r tions 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 cretion, and sensitivity of affected tissues.
tion is not mature in newborn rats (626), do
(643), and guinea pigs (1256). Indirect evid
newborn humans also have a decreased c
crete foreign compounds into bile (1206).
The d

(643), and guinea pigs (1256). Indirect evidence indicates
newborn humans also have a decreased capacity to ex-
crete foreign compounds into bile (1206).
The decreased excretion of ouabain in newborn rats
has been extensi 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 neonata crete foreign compounds into bile (1206). So a summer that the decreased excretion of ouabain in newborn rats that hes been extensively studied and reviewed (650). Results are indicate that neonatal rat liver is unable to The decreased excretion of ouabain in newborn rats thas been extensively studied and reviewed (650). Results andicate that neonatal rat liver is unable to extract ouabain from plasma which enables ouabain to produce its st has been extensively studied and reviewed (650). Results and
indicate that neonatal rat liver is unable to extract oua-
bain from plasma which enables ouabain to produce its stu
toxic effects (625). This relative inability indicate that neonatal rat liver is unable to extract oua-
bain 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 be

BILE FORMATION, HEPATIC UPTAKE, AND BILIARY EXCRETION 35
emale or male rats $(50 \,\mu\text{l/min}/\text{and taurocholate}$ (629, 631, 645, 650, 670). The excretory
pendent and independent frac- capacity approaches adult levels by 1 month of age KE, AND BILIARY EXCRETION 35
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 3
and taurocholate (629, 631, 645, 650, 670). The excretor
capacity approaches adult levels by 1 month of age an
can be stimulated to develop earlier by pretreatmen
with microsomal enzyme inducers (637, 645). Decrease 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 he 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
he 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 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).
 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
i 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 l 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
 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 isolated from 12-day-old rats, thus suggesting that a
hepatic uptake capacity is probably the mechanism
which ouabain exhibits greater toxicity in the new
rat (1118). Thus, a decreased uptake process appear
be responsible patic uptake capacity is probably the mechanism b
nich ouabain exhibits greater toxicity in the newbor
t (1118). Thus, a decreased uptake process appears t
responsible for differences in toxicity of ouabain.
Neonatal rats

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 phalrat (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 phal-
loidin (1296). Decreased sensitivity of the 5-day-old be responsible for differences in toxicity of ouabain.
Neonatal rats are tolerant to the toxic effects of phal-
loidin (1296). Decreased sensitivity of the 5-day-old rats
is not caused by lack of microfilaments (19). Isola 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 b loidin (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 ³H-demethylphalloin (918, 1296).
S is not caused by lack of microfilaments (19). Isolated
hepatocytes from newborns exhibit reduced uptake of
both bile acids and ³H-demethylphalloin (918, 1296).
Since phalloidin is not biotransformed in the liver (950),
 hepatocytes from newborn
both bile acids and ³H-de
Since phalloidin is not biot
tolerance is apparently du
toxin (1295, 1296).
Depressed uptake in new th bile acids and ³H-demethylphalloin (918, 1296).
nce phalloidin is not biotransformed in the liver (950),
lerance is apparently due to decreased uptake of the
xin (1295, 1296).
Depressed uptake in neonatal animals has

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 ob-
served for other xenobiotics. Cumulati tolerance is apparently due to decreased uptake of the
toxin (1295, 1296).
Depressed uptake in neonatal animals has been ob-
served for other xenobiotics. Cumulative hepatic uptake
of bilirubin is low in young guinea pigs toxin (1295, 1296).

Depressed uptake in neonatal animals has been of

served for other xenobiotics. Cumulative hepatic upta

of bilirubin is low in young guinea pigs and does ne

achieve adult capacity until 15 days of ag Depressed uptake in neonatal animals has been ob
served for other xenobiotics. Cumulative hepatic uptake
of bilirubin is low in young guinea pigs and does no
achieve adult capacity until 15 days of age (381). Accu
mulation 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 new-
born guinea pigs is lower than that in slices from adults of bilirubin is low in young guinea pigs and does not
achieve adult capacity until 15 days of age (381). Accu-
mulation of indocyanine green in liver slices from new-
born guinea pigs is lower than that in slices from adul achieve adult capacity until 15 days of age (381). Accumulation of indocyanine green in liver slices from new-
born guinea pigs is lower than that in slices from adults
(522). Moreover, the transport maximum for indocyanin (523). rn guinea pigs is lower than that in slices from adults
22). Moreover, the transport maximum for indocyanine
een is one-third the adult level in neonatal guinea pigs
23).
Hepatic uptake of taurocholate in fetal sheep is si

(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 ex green is one-third the adult level in neonatal guinea pigs (523).

(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 (523).
Hepatic uptake of taurocholate in fetal sheep is simila
to that in adults. However, adult liver excretes the trace
dose more rapidly than fetal or neonatal liver which
indicates that hepatic bile acid transport is n 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 co dose more rapidly than fetal or neonatal liver which excretion in 20-day-old rats (338). The ability of neonatal 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 pletely 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 betw 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 capac 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 ts to excrete methylmercury into bile develops between
and 4 weeks of age and correlates with the capacity of
e liver to secrete glutathione (62). Excretory transport
ay be limited by the available concentration of GSH.
Th

tion is not mature in newborn rats (626) , dogs and rabbits of excretion in 10- and 35-day-old rats indicates higher (643) , and guinea pigs (1256) . Indirect evidence indicates plasma and liver concentrations and lowe 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 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 functi 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 bil 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 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. Compari (519, 520). About 68% of colchicine is excreted into bily 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 h 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 exc 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 excre-
tion rates for colchicine in the immature rats. R 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 o plasma and liver concentration
tion rates for colchicine in the
suggest colchicine is more toxi
the lower capacity of the liver
and excrete it into bile (519).
Excretion of drugs by the l In rates for colchicine in the immature rats. Results
ggest colchicine is more toxic to newborns because of
e lower capacity of the liver to concentrate colchicine
d excrete it into bile (519).
Excretion of drugs by the li

suggest colchicine is more toxic to newborns because
the lower capacity of the liver to concentrate colchic
and excrete it into bile (519).
Excretion of drugs by the liver into bile cannot
studied directly in newborn rats. logical development of the biliary tract in rats has been
studied directly in newborn rats. However, the morpho-
logical development of the biliary tract in rats has been
described as an indirect estimate of biliary functi 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)

aspet

forming and is defined by an intracellular invagination **EXELAASSEN AND V**
forming and is defined by an intracellular invagination duc
of two adjacent cell membranes into one of the two add
neighboring hepatocytes. The canalicular lumen dilates or a KLAASSEN ANI
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 reg forming and is defined by an intracellular invagination duce
of two adjacent cell membranes into one of the two add
neighboring hepatocytes. The canalicular lumen dilates or a
during the first 3 days postpartum but then re 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
nor of two adjacent cell membranes into one of the two a
neighboring hepatocytes. The canalicular lumen dilates of
during the first 3 days postpartum but then regresses to
normal size and fills with microvilli by day 10. Howe 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 depres 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 struct uptake and/or conjugation. 10 days of age. If adult-like canalicular structure coids iffects secretory function, then maturation of excretory rubin increase in serum take and/or conjugation. wiously 4. Fasting. Fasting induces a slight increase in s

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 function following day 10 must be due to development c
uptake and/or conjugation.
4. Fasting. Fasting induces a slight increase in serur
bilirubin concentration in normal humans and patient
with hemolytic jaundice $(78, 3$ 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 abso-

lute rise in serum bili 4. Fasting induces a slight increase in serum
bilirubin concentration in normal humans and patients
with hemolytic jaundice (78, 331). A much greater abso-
lute rise in serum bilirubin concentration occurs after
fasting i bilirubin concentration in normal humans and patients
with hemolytic jaundice (78, 331). A much greater abso-
lute rise in serum bilirubin concentration occurs after
fasting in patients with Gilbert's syndrome (93, 334) a 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 hepat lute rise in serum bilirubin concentration occurs after
fasting in patients with Gilbert's syndrome (93, 334) and
reppears to result from an acquired depression of hepatic
bilirubin UDP-glucuronosyltransferase activity (33 fasting in patients with Gilbert's syndrome (93, 334) a
appears to result from an acquired depression of hepa
bilirubin UDP-glucuronosyltransferase activity (3:
332). A similar increase in plasma bilirubin is observ
in pon bilirubin UDP-glucuronosyltransferase activity (331, 332). A similar increase in plasma bilirubin is observed
in ponies under food deprivation (300). Caloric restric-
tion is responsible for diet-induced hyperbilirubinemia bilirubin UDP-glucuronosyltransferase activity (3
332). A similar increase in plasma bilirubin is obser
in ponies under food deprivation (300). Caloric rest:
tion is responsible for diet-induced hyperbilirubine
but not alt 332). A similar increase in plasma bilirubin is observed in ponies under food deprivation (300). Caloric restriction is responsible for diet-induced hyperbilirubinem but not alterations in dietary components of carboh dra 332). A simuar increase in plasma bilitubin is observed
in ponies under food deprivation (300). Caloric restric-
tion is responsible for diet-induced hyperbilirubinemia
but not alterations in dietary components of carbohy but not alterations in dietary components of carbohy-

More recent studies indicate that depressed carbohy-
drate reserves can affect bilirubin conjugation. Fasting
produced a 50% inhibition of UDP-glucose dehydrogedrates, protein, or fat (330). Hepatic clearance of biliru-
bin (300, 608), BSP and indocyanine green (1129), and
bile acids (299) is decreased during fasting.
More recent studies indicate that depressed carbohy-
drate re bin (300, 608), BSP and indocyanine green (1129),
bile acids (299) is decreased during fasting.
More recent studies indicate that depressed carbo
drate reserves can affect bilirubin conjugation. Fas
produced a 50% inhibiti bile acids (299) is decreased during fasting.

More recent studies indicate that depressed carbohy-

drate reserves can affect bilirubin conjugation. Fasting

produced a 50% inhibition of UDP-glucose dehydroge-

nase acti More recent studies indicate that depressed carbohy-
drate reserves can affect bilirubin conjugation. Fasting
produced a 50% inhibition of UDP-glucose dehydroge-
nase activity resulting in a 43% decrease in hepatic
UDPGA c drate reserves can affect bilirubin conjugation. Fasting
produced a 50% inhibition of UDP-glucose dehydroge-
nase activity resulting in a 43% decrease in hepatic
UDPGA concentration in rats (333). Furthermore, nu-
trition produced a 50% inhibition of UDP-glucose dehydroge-
nase activity resulting in a 43% decrease in hepatic
UDPGA concentration in rats (333). Furthermore, nu-
tritional states can alter UDPGA levels which affects the
glucuro nase activity resulting in a 43% decrease in hepatic
UDPGA concentration in rats (333). Furthermore, nu-
tritional states can alter UDPGA levels which affects the
glucuronidation of p-nitrophenol in isolated rat liver
(973 UDPGA concentration in rats (333). Furthermore, nu-
tritional 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 in-
c 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 acetaminophenglucuromaation of p-introphenof in isolated rat liver

(973, 974). Short-term fasting (48 hours) can also in-

crease the turnover of hepatic GSH and decrease its

concentration in livers from control or acetaminophen-

pr crease 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
xenobioti expectively affect other factors of metabolism such as

markedly affect other factors of metabolism such as

xenobiotic transport, oxygen or energy states, NAD or yill

NADP concentrations as well as the major phase I and 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). arkedly affect other factors of metabolism such
nobiotic transport, oxygen or energy states, NAD
ADP concentrations as well as the major phase I a
njugation pathways (1179).
However, the complete mechanism of fasting hype

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 hyper-
bilirubinemia is not totally underst NADP concentrations as well as the major phase I and
conjugation pathways (1179).
However, the complete mechanism of fasting hyper-
bilirubinemia is not totally understood. For example,
data obtained in fasting subjects wi conjugation pathways (1179).

However, the complete mechanism of fasting hyper-

bilirubinemia is not totally understood. For example,

data obtained in fasting subjects with Gilbert's syndrome

suggest there was no modifi However, the complete mechanism of fasting hyper-
bilirubinemia is not totally understood. For example,
data obtained in fasting subjects with Gilbert's syndrome
suggest there was no modification in bilirubin clearance
pa bilirubinemia is not totally understood. For examp
data obtained in fasting subjects with Gilbert's syndrom
suggest there was no modification in bilirubin clearar
but rather an increased intrahepatic production of b
pigmen 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 c suggest there was no modification in bilirubin clearance ra
but rather an increased intrahepatic production of bile 3 -
pigment (870). These results are at variance with conclu-
desions made by several laboratories (93, but rather an increased intrahepatic production of bile 3-methylcholanthrene. Other studies have demonstrated
pigment (870). These results are at variance with conclu-
sions made by several laboratories (93, 331, 333, 608 decreased after fasting (1129).

1129). In addition, the plasma disappearance and biliary trea
excretion of BSP, which is not glucuronidated, are also osyl
decreased after fasting (1129). by 2
Results of a recent study suggest alterations in uptake $2,3$ fact
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 ap-
pear to exist: a becreased after fasting (1125).
Results of a recent study suggest alterations in uptake 2,5
account for the diminished clearance of BSP (708). In
fasted rats, two distinct carriers for organic anions ap-
pear to exist: a h results of a fecent study suggest alterations in uptake
account for the diminished clearance of BSP (708). In
fasted rats, two distinct carriers for organic anions ap-
pear to exist: a high affinity, Na⁺-dependent system account for the diminished clearance of BSF (706). In
fasted rats, two distinct carriers for organic anions ap-
pear to exist: a high affinity, Na⁺-dependent system and
a low affinity, Na⁺-independent system. Although

normal size and fills with microvilli by day 10. However, results from a fasting-induced decrease in hepatic ligan-
hepatic excretory function in the rat remains depressed din concentration (1129). Administration of glucoc D WATKINS
duced the capacity of the high affinity site 50%. In
addition, a slight depression of hepatic blood flow and/ D WATKINS
duced 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 D WATKINS
duced 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 pr duced 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
res duced the capacity of the high affinity site 50%. I
addition, a slight depression of hepatic blood flow and
or an increase in BSP efflux may also affect the plasm
clearance of BSP. The higher rate of efflux probab
results addition, a slight depression of hepatic blood flow a
or an increase in BSP efflux may also affect the pla
clearance of BSP. The higher rate of efflux prob-
results from a fasting-induced decrease in hepatic lig
din concen 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 ligan-
din concentration (1129). Administration of glucocorticlearance of BSP. The higher rate of efflux probably
results from a fasting-induced decrease in hepatic ligan-
din concentration (1129). Administration of glucocorti-
coids increases the hepatic clearance and uptake of bil results from a fasting-induced decrease in hepatic ligandin concentration (1129). Administration of glucocorticoids increases the hepatic clearance and uptake of bili-
rubin but does not influence the biliary excretion of din concentration (1129). Administration of glucocortic-
coids increases the hepatic clearance and uptake of bili-
rubin but does not influence the biliary excretion of the
pigment in patients with Gilbert's syndrome (866) coids increases the hepatic clearance and uptake cordin but does not influence the biliary excretion
pigment in patients with Gilbert's syndrome (866
viously, the effects of fasting on biliary excretio
complex and may affe rubin but does not
pigment in patient
viously, the effect
complex and may
tion of xenobiotics
5. Pregnancy. T viously, 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 se

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 tion 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 f 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
impaire 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 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
 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
(6 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
 is enhanced (979, 982). Biliary excretio
estrogenic chemicals (16), progester
(699), cholic and chenodeoxycholic aci
lipids (980), diphenylhydantoin (1219,
(982) is depressed in pregnant animals.
In the hamster, pregnancy trogenic chemicals (16), progesterone metabol
99), cholic and chenodeoxycholic acids (700), bilids (980), diphenylhydantoin (1219, 1222), and H
82) is depressed in pregnant animals.
In the hamster, pregnancy decreased bile

(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-inde-
pendent flo lipids (980), diphenylhydantoin (1219, 1222), and BSP (982) is depressed in pregnant animals.

In the hamster, pregnancy decreased bile acid-inde-

pendent flow, hepatic $Na^+.K^+.ATP$ ase activity and

cholic acid excretion, (982) is depressed in pregnant animals.
In the hamster, pregnancy decreased bile acid-inde-
pendent flow, hepatic $Na^+ \cdot K^+ \cdot ATP$ as activity and
cholic acid excretion, and increased the concentration of
biliary lipids wit In the hamster, pregnancy decreased bile acid-inde-
pendent flow, hepatic $Na^+ - K^+$ -ATPase activity and
cholic acid excretion, and increased the concentration of
biliary lipids without altering the lithogenic index (980). pendent 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 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 r Henry lipids without altering the lithogenic index (980).

The decrease in cholic acid excretion accounts for the

minished secretion of total bile acids and part of the

crease in bile flow.

When examined in pregnant ra

affects biliary excretory function in several ways: BSP
retartion is increased while its transport maximum is
depressed; the extraction of bilirubin from plasma is
impaired and the serum activity of alkaline phosphatase
is 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 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 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, 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 the isolated perfused liver, biliary concentration of
phenyl-5-p-hydroxyphenylhydantoin glucuronide,
primary metabolite of diphenylhydantoin, was decrea
and the liver had apparently lost its ability to concentr
the metabol 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 diphe and the liver had apparently lost its ability to concentrate
the metabolite in bile (1222). Similar effects on diphen-
ylhydantoin metabolism and excretion can be observed and the liver had apparently lost its ability to concentrate
the metabolite in bile (1222). Similar effects on diphen-
ylhydantoin metabolism and excretion can be observed
in the isolated perfused rat liver and in vivo fo the metabolite in bile (1222). Simi
ylhydantoin metabolism and excre
in the isolated perfused rat liver a
administration of estradiol-17 β (12
estrogen, diethylstilbestrol (817).
UDP-glucuronosyltransferase ac hydantoin metabolism and excretion can be observed
the isolated perfused rat liver and in vivo following
ministration of estradiol-17 β (1220), and the synthetic
trogen, diethylstilbestrol (817).
UDP-glucuronosyltransfe administration of estradiol-17 β (1220), and the synthetic estrogen, diethylstilbestrol (817).
UDP-glucuronosyltransferase activity toward estrone

Results of a recent study suggest alterations in uptake 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in pregnant
count for the diminished clearance of BSP (708). In rats (142). Moreover, estradiol depressed the biliary ex-
s administration of estradiol-17 β (1220), and the synthetic
estrogen, diethylstilbestrol (817).
UDP-glucuronosyltransferase activity toward estrone
and estradiol was decreased by 30% in pregnant rats and
rabbits (1221) b 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. 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
depr rabbits (1221) but was more susceptible to induction by rabbits (1221) but was more susceptible to inducti
3-methylcholanthrene. Other studies have demons
depression of glucuronide conjugation of steroids
non-steroidal acceptors (840, 1221). Pregnancy an
treatment with estradi 3-methylcholanthrene. Other studies have demonstrated
depression of glucuronide conjugation of steroidal and
non-steroidal acceptors (840, 1221). Pregnancy and pre-
treatment with estradiol-17 β decreased UDP-glucuron-
 depression of glucuronide conjugation of steroidal and
non-steroidal acceptors (840, 1221). Pregnancy and pre-
treatment with estradiol-17 β decreased UDP-glucuron-
osyltransferase activities toward morphine and estrone non-steroidal acceptors (840, 1221). Pregnancy and pre-
treatment with estradiol-17*β* decreased UDP-glucuron-
osyltransferase activities toward morphine and estrone
by 20% and 50%, respectively, and could be induced by
2, treatment with estradiol-17 β decreased UDP-glucuron-
osyltransferase 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
r osyltransferase 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 ex-
 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 bi 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in pregnant
rats (142). Moreover, estradiol depressed the biliary ex-
cretion of morphine 3-glucuronide but did not affect bile
flow (142). In contrast, pregnancy reduced bile flo rats (142). Moreover, estradiol depressed the biliary excretion of morphine 3-glucuronide but did not affect bil
flow (142). In contrast, pregnancy reduced bile flow
slightly but did not alter the excretion of morphine
The cretion 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 preg-

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BILE FORMATION, HEPATIC UPTAK
vary with the chemical and the dose and duration of irestrogen exposure. vary with the che
estrogen exposure. **EXAMELY WE SILE FORMATION, HEFA.**
 C. Pharmacological Factors Influencing Biliary
 C. Pharmacological Factors Influencing Biliary
 Excretion of Xenobiotics

estrogen exposure.
C. Pharmacological Factors Influencing Biliary
Excretion of Xenobiotics

11. *Pharmacological Factors Influencing Biliary*

1. *Microsomal Enzyme Inducers*. Chemicals that in-

1. *Microsomal Enzyme Inducers*. Chemicals that in-

1. *Microsomal Enzyme Inducers*. Chemicals that in-

1. *Microsom* C. Pharmacological Factors Influencing Biliary
Excretion of Xenobiotics
1. Microsomal Enzyme Inducers. Chemicals that in-
crease the synthesis of various metabolizing enzymes
affect the hepatobiliary disposition of xenobio Excretion of Xenobiotics

1. Microsomal Enzyme Inducers. Chemicals that in-

crease the synthesis of various metabolizing enzymes

affect the hepatobiliary disposition of xenobiotics. These

agents may produce their actio Extretion of *Xeniobotics*
1. Microsomal Enzyme Inducers. Chemicals that in-
crease the synthesis of various metabolizing enzymes
affect the hepatobiliary disposition of xenobiotics. These
agents may produce their actions 1. Microsomal Enzyme Inducers. Chemicals that in-
crease the synthesis of various metabolizing enzymes
affect the hepatobiliary disposition of xenobiotics. These
agents may produce their actions by influencing one or
more crease 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, affect the hepatobiliary disposition of xenobiotics. These benzo
agents may produce their actions by influencing one or Exte
more of the following factors: hepatic blood flow rate,
uptake into the hepatocyte, biotransforma rate. ore of the following factors: hepatic blood flow rate,
take into the hepatocyte, biotransformation and/or
tracellular storage, transport into bile, and bile flow
te.
Changes in hepatic blood flow can markedly alter
patic e

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
 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). Administra 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 effic Changes in hepatic blood flow can markedly alt
hepatic extraction of chemicals having a high intrins
clearance (1164, 1263) (see section VI B). Administratic
of microsomal enzyme inducers increases the efficien
of hepatic 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 el clearance (1164, 1263) (see section VI B). Administration
of microsomal enzyme inducers increases the efficiency
of hepatic extraction (867, 868), and both plasma elimi-
nation and half-life of drugs with high extractions of microsomal enzyme inducers increases the efficiency
of hepatic extraction (867, 868), and both plasma elimi-
nation and half-life of drugs with high extractions depend
on hepatic blood flow rate. Alteration of blood fl 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
 nation 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); inon hepatic blood flow rate. Alteration of blood flow by
phenobarbital was suggested to be the mechanism for
the enhanced clearance of indocyanine green (784); in-
creases in blood flow and intrinsic clearance were directl phenobarbital was suggested to be the mechanism for
the enhanced clearance of indocyanine green (784); in-
creases in blood flow and intrinsic clearance were directly
proportional to the increase in liver mass. However, i 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 creases 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 proportional to the increase in liver mass. However, has recently been demonstrated that indocyanine gredoes not have high intrinsic clearance in the rat (52 and earlier that phenobarbital does not enhance to plasma disapp has recently been demonstrated
does not have high intrinsic cl
and earlier that phenobarbita
plasma disappearance and bili
anine green (344, 621).
Microsomal enzyme inducers es not have high intrinsic clearance in the rat (526)
d earlier that phenobarbital does not enhance the
asma disappearance and biliary excretion of indocy-
ine green $(344, 621)$.
Microsomal enzyme inducers could affect

and earlier that phenobarbital does not enhance the
plasma disappearance and biliary excretion of indocy-
anine green (344, 621).
Microsomal enzyme inducers could affect the uptake
of xenobiotics into hepatocytes. Phenoba anine green $(344, 621)$.
Microsomal enzyme inducers could affect the uptake
of xenobiotics into hepatocytes. Phenobarbital, 3-
methylcholanthrene, and pregnenolone-16 α -carbonitrile
(PCN) affect hepatic uptake of ouaba Microsomal enzyme inducers could affect the uptake
of xenobiotics into hepatocytes. Phenobarbital, 3-
methylcholanthrene, and pregnenolone-16 α -carbonitrile
(PCN) affect hepatic uptake of ouabain, PAEB, and
taurocholate of xenobiotics into hepatocytes. Phenobarbital, 3-
methylcholanthrene, and pregnenolone-16 α -carbonitrile
(PCN) affect hepatic uptake of ouabain, PAEB, and
taurocholate differently (286). Phenobarbital and PCN
significa methylcholanthrene, and pregnenolone-16 α -carbonitrile (PCN) affect hepatic uptake of ouabain, PAEB, and taurocholate differently (286). Phenobarbital and PCN significantly increase the initial velocity of uptake of oua (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) 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
enhan 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 do 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 i (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 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 proces intracellular concentrations (286). Results suggest that bile-3-methylcholanthrene inhibits the excretory processes dreptor these substrates. PCN enhances ouabain and not taurocholate uptake, which further indicates indepe 3-methylcholanthrene inhibits the excretory processes
for these substrates. PCN enhances ouabain and not
taurocholate uptake, which further indicates independ-
ent transport systems for bile acids and ouabain. The
data sug for these substrates. PCN enhances ouabain and not
taurocholate uptake, which further indicates independ-
ent transport systems for bile acids and ouabain. The
data suggest that these microsomal enzyme inducers
increase th urocholate uptake, which further indicates independ-
t transport systems for bile acids and ouabain. The
ta suggest that these microsomal enzyme inducers
rease the number of carriers for transport into liver.
Many microsom

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 i increase the number of carriers for transport into liver. the Many microsomal enzyme inducers increase liver it weight, and the mechanism first proposed to explain the pincrease in bile flow produced by phenobarbital was t 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
doe increase in bile flow produced by phenobarbital was that tion into bile of metabolites of N-N-dimethyl-4-amino-
it increased liver weight (992). For several reasons this azobenzene (DAB). Conversely, mixed-function oxidase increase in bile flow produced by phenobarbital was that
it increased liver weight (992). For several reasons this azobe
does not appear to be correct. First, biliary flow and liver inhib
weight do not increase at the same it increased liver weight (992). For several reasons this azob
does not appear to be correct. First, biliary flow and liver
weight do not increase at the same rate. Biliary flow is whice
significantly elevated 24 hours aft 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 administrat weight do not increase at the same rate. Biliary flow
significantly elevated 24 hours after one dose and reace
a plateau between 2 and 7 days of administrati
whereas liver weight is not significantly elevated a
one dose of 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 through-

BILE FORMATION, HEPATIC UPTAKE, AND BILIARY EXCRETION 37
and the dose and duration of increase to the same extent. While phenobarbital pro-
duces about a 50% increase in bile flow, it only increases liver weight 15% to 25% (619). Finally, the abilities of LIMET AND BILIARY EXCRETION 37
increase to the same extent. While phenobarbital pro-
duces about a 50% increase in bile flow, it only increases
liver weight 15% to 25% (619). Finally, the abilities of
various microsomal e 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 increa 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
w duces 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 hver 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 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 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 (flow are produced by 3-methylcholanthrene and

flow are produced by 3-methylcholanthrene a
benzo(a)pyrene (619, 620).
Extensive studies on the effects of barbiturates
biliary excretion have been reviewed (159, 640, 64
Stimulation of bile flow does not correlate with m 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 micro-
somal enzyme induction; the incre Extensive studies on the effects of barbiturates on
biliary excretion have been reviewed (159, 640, 648).
Stimulation of bile flow does not correlate with micro-
somal enzyme induction; the increase in bile flow occurs
ear biliary excretion have been reviewed (159, 640, 648).
Stimulation of bile flow does not correlate with micro-
somal enzyme induction; the increase in bile flow occurs
earlier than the rise in P-450 (158, 184, 339, 341). Wh somal 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 earlier than the rise in P-450 (158, 184, 339, 341). While 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 phenob cobaltous chloride, an inducer of heme oxygenase, blocks
the increase in cytochrome P-450 produced by pheno-
barbital, it does not prevent the choleresis. The pheno-
barbital-mediated increase in bile flow is due to an inthe increase in cytochrome P-450 produced by pheno-
barbital, it does not prevent the choleresis. The pheno-
barbital-mediated increase in bile flow is due to an in-
crease in bile salt-independent flow (102, 622), which
m barbital-mediated increase in bile flow is due to an in-
crease in bile salt-independent flow (102, 622), which
may be due to stimulation of $\text{Na}^+\text{-K}^+\text{-ATPase}$ (935, 968,
1091). However, the role of $\text{Na}^+\text{-K}^+\text{-ATPase$ barbital-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 crease in bile salt-independent flow (
may be due to stimulation of $Na^+ \cdot K^+ \cdot A$
1091). However, the role of $Na^+ \cdot K^+ \cdot A$
mation is controversial and some author
an increase after phenobarbital (595).
Once in the hepato ay be due to stimulation of $Na^+ \cdot K^+ \cdot ATP$ ase (935, 968
91). However, the role of $Na^+ \cdot K^+ \cdot ATP$ ase in bile for
ation is controversial and some authors have not seen
increase after phenobarbital (595).
Once in the hepatoc

mine green (344, 621).

Microsomal enzyme inducers could affect the uptake

of xenobiotics into hepatocytes. Phenobarbital, 3-

methylcholanthrene, and pregnenolone-16 α -carbonitrile

(PCN) affect hepatic uptake of ouab 1091). However, the role of Na^+ -K⁺-ATPase in bile for-
mation is controversial and some authors have not seen
an increase after phenobarbital (595).
Once in the hepatocyte, binding to intracellular com-
ponents can fa 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, an increase after phenobarbital (595).

Once in the hepatocyte, binding to intracellular com-

ponents can facilitate accumulation of a chemical in the

liver cell. The importance of two such proteins, ligandin

and metall 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, ma ponents 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 li 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 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
ind 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 does not bind to these components. For example, odaba
does not bind to ligandin (638) yet microsomal enzym
inducers enhance its biliary excretion. Also, the amous
of ligandin in liver is not related to the increased bilia
 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). Stim-
ulation of the enzymatic properties of ligandin (GSH S-
transferase) by butylated hydroxyanisole and *tra* excretion after microsomal enzyme inducers (638). Stimulation of the enzymatic properties of ligandin (GSH S-
transferase) by butylated hydroxyanisole and *trans*-stil-
bene oxide enhances the biliary excretion of BSP preexcretion after microsomal enzyme inducers (638). Stim-
ulation of the enzymatic properties of ligandin (GSH S-
transferase) by butylated hydroxyanisole and *trans*-stil-
bene oxide enhances the biliary excretion of BSP pr ulation of the enzymatic properties of ligandin (GSH S-
transferase) by butylated hydroxyanisole and *trans*-stil-
bene oxide enhances the biliary excretion of BSP pre-
sumably by increasing the rate of conjugation (429). transferase) by butylated hydroxyanisole and *trans*-stil-
bene oxide enhances the biliary excretion of BSP pre-
sumably by increasing the rate of conjugation (429). It
appears that the ligandin induced by microsomal enzym bene oxide enhances the biliary excretion of BSP pre-
sumably 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 drugs. pears that the ligandin induced by microsomal enzym
ducers is more important as an enzyme than as
nding protein in enhancing the biliary excretion
ugs.
The importance of biotransformation in biliary excre-
nn is well known

ent transport systems for bile acids and ouabain. The more water soluble by phase I and phase II metabolic
data suggest that these microsomal enzyme inducers reactions, and phase II reactions significantly increase
increas 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 excre-
tion is well known (733). Most xenobiotics are made
more 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
reac 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
t 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 mole 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
 more water soluble by phase I and phase II metabol
reactions, and phase II reactions significantly increa
the molecular weight of the xenobiotic thereby enhancii
its elimination. For example, 3-methylcholanthrene an
phenob reactions, and phase II reactions significantly
the molecular weight of the xenobiotic thereby e
its elimination. For example, 3-methylcholanth
phenobarbital pretreatments stimulate the rate
tion into bile of metabolites o the molecular weight of the xenobiotic thereby enhancing
its elimination. For example, 3-methylcholanthrene and
phenobarbital pretreatments stimulate the rate of excre-
tion into bile of metabolites of N-N-dimethyl-4-amino its elimination. For example, 3-methylcholanthrene and
phenobarbital pretreatments stimulate the rate of excre-
tion into bile of metabolites of N-N-dimethyl-4-amino-
azobenzene (DAB). Conversely, mixed-function oxidase
in phenobarbital pretreatments stimulate the rate of excretion into bile of metabolites of N-N-dimethyl-4-amino
azobenzene (DAB). Conversely, mixed-function oxidas
inhibitors, SKF 525A and piperonylbutoxide, and agent
which d tion into bile of metabolites of N-N-dimethyl-4-amino-
azobenzene (DAB). Conversely, mixed-function oxidase
inhibitors, SKF 525A and piperonylbutoxide, and agents
which deplete GSH, diethyl maleate and iodomethane,
decreas azobenzene (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
rateinhibitors, 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) al-
tho which deplete GSH, diethyl maleate and iodomethane
decrease biliary excretion. Metabolism appears to be the
rate-limiting step in the elimination of DAB (735) al
though conjugation with GSH is also involved; late
studies s though 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-acri-88

formation also affect the biliary excretion of 4'-(9-acri-

dinylamino)methanesulfon-m-anisidide (1084), valproic (

acid (1236), hexachlorophene (653), and many other c ELAASSEN AN
formation also affect the biliary excretion of 4'-(9-acri-
dinylamino)methanesulfon-m-anisidide (1084), valproic
acid (1236), hexachlorophene (653), and many other
chemicals. Administration of phenobarbital to formation also affect the biliary excretion of $4'$ -(9-acri-
dinylamino)methanesulfon-*m*-anisidide (1084), valproic (2
acid (1236), hexachlorophene (653), and many other or
chemicals. Administration of phenobarbital to c dinylamino)methanesulfon-m-anisidide (1084), valproic
acid (1236), hexachlorophene (653), and many other
chemicals. Administration of phenobarbital to children
with intrahepatic cholestasis reduces the concentration emicals. Administration of phenobarbital to child
th intrahepatic cholestasis reduces the concentrat
bile acids in serum and increases that of bile a
acuronides in bile (1137).
Administration of phenobarbital, clofibrate,

glucuronides in bile (1137).
Administration of phenobarbital, clofibrate, spirono-
lactone. or PCN to male and female rats stimulates the with intrahepatic cholestasis reduces the concentration (76
of bile acids in serum and increases that of bile acid me
glucuronides in bile (1137).
Administration of phenobarbital, clofibrate, spirono-
lactone, or PCN to ma of bile acids in serum and increases that of bile acid neutronides in bile (1137).

Administration of phenobarbital, clofibrate, spirono-

lactone, or PCN to male and female rats stimulates the deplasma clearance of biliru exoger

exoger

Administration of phenobarbital, clofibrate, spirono-

lactone, or PCN to male and female rats stimulates the

cludes

plasma clearance of bilirubin and its biliary excretion

(558, 771, 952, 992, 1110, 130 Administration of phenobarbital, clofibrate, spirono-
lactone, or PCN to male and female rats stimulates the
plasma clearance of bilirubin and its biliary excretion d
(558, 771, 952, 992, 1110, 1300). PCN enhances rat live lactone, or PCN to male and female rats stimulates the diplasma clearance of bilirubin and its biliary excretion diffeored (558, 771, 952, 992, 1110, 1300). PCN enhances rat liver ratio UDP-glucuronosyltransferase activity 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 (558, 771, 952, 992, 1110, 1300). PCN enhances rat liver
UDP-glucuronosyltransferase activity toward bilirubin fl
(1233, 1237). Furthermore, spironolactone induction of p
UDP-glucuronosyltransferase increases the conjugat UDP-glucuronosyltransferase activity toward bilirul (1233, 1237). Furthermore, spironolactone induction UDP-glucuronosyltransferase increases the conjugatiof phenolphthalein and *p*-nitrophenol as well as bilirul (807). Th (1233, 1237). Furthermore, spironolactone induction of UDP-glucuronosyltransferase increases the conjugation of phenolphthalein and p -nitrophenol as well as bilirubition (807). These examples further demonstrate the imp biotics. phenolphthalein and *p*-nitrophenol as well as bilirubin
07). These examples further demonstrate the impor-
nce of metabolism on the biliary excretion of xeno-
tics.
Administration of spironolactone to rats also increases

(807). These examples further demonstrate the importance of metabolism on the biliary excretion of xeno-
biotics.
Administration of spironolactone to rats also increases
the biliary excretion of several cardiac glycosides tance of metabolism on the biliary excretion of xeno-
biotics.
Administration of spironolactone to rats also increases
the biliary excretion of several cardiac glycosides (168,
169, 636), indomethacin (647), and various me biotics.

Administration of spironolactone to rats also increase

the biliary excretion of several cardiac glycosides (168

169, 636), indomethacin (647), and various metals (453-

455, 616, 641, 654). Specifically, when i 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 the biliary excretion of several cardiac glycosides (168
169, 636), indomethacin (647), and various metals (453-
455, 616, 641, 654). Specifically, when injected 15 min
utes before mercuric chloride, spironolactone stimula 169, 636), indomethacin (647), and various metals (453– $(28455, 616, 641, 654)$. Specifically, when injected 15 min-
utes before mercuric chloride, spironolactone stimulates spectre plasma disappearance and biliary secret Foo, 010, 041, 004). Specifically, when injected to infin-
utes before mercuric chloride, spironolactone stimulates
the plasma disappearance and biliary secretion of mer-
cury. This effect of spironolactone is too rapid to the plasma disappearance and biliary secretion of n cury. This effect of spironolactone is too rapid to explained by induction of microsomal enzymes. Appently, the spironolactone metabolite, thioacetic a complexes the meta cury. 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 th 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 lo ently, the spironolactone metabolite, thioacetic acid, phonometas is complexes the metal and causes it to distribute through-
out the body in similar fashion to organic mercurials and
with lower plasma and kidney concentra complexes the metal and causes it to distribute through-
out 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 th out the body in similar fashion to organic mercurials and with lower plasma and kidney concentrations and higher levels in blood and other tissues (641). The metal is then an excreted into bile as a low-molecular weight co with lower plasma and kidney concentrations and higher
levels in blood and other tissues (641). The metal is there
excreted into bile as a low-molecular weight complex
(1182). However, spironolactone does not influence the excreted into bile as a low-molecular weight complex (456, 1062, 1063, 1287) but not BSP or DBSP (1287).
(1182). However, spironolactone does not influence the The polychlorinated biphenyls are generally regarded as
excret excreted into bile as a low-molecular weight complex (1182). However, spironolactone does not influence the Texcretion of all metals similarly. For example, the concentrations of mercury and copper in kidney and plasma mor 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
 centrations of mercury and copper in kidney and pla
were lower after spironolactone and excretion into
was increased three- and sevenfold. Spironolactone
not alter the distribution or biliary excretion of l
manganese or ar were lower after spironolactone and excretion into bile of
was increased three- and sevenfold. Spironolactone does
not alter the distribution or biliary excretion of lead,
manganese or arsenic, increases the kidney concent was increased three- and sevenfold. Spironolactone does
not alter the distribution or biliary excretion of lead,
manganese or arsenic, increases the kidney concentra-
tion of cadmium and silver, and decreases the biliary
e manganese or arsenic, increases the kidney concentra-

tion of cadmium and silver, and decreases the biliary

elimination of silver (654).

Microsomal enzyme inducers also stimulate the excre-

(7

tion of several nonmetab

tion of cadmium and silver, and decreases the biliary
elimination of silver (654).
Microsomal enzyme inducers also stimulate the excre-
tion of several nonmetabolized organic compounds. More
than a decade ago phenobarbital elimination of silver (654).

Microsomal enzyme inducers also stimulate the excretion of several nonmetabolized organic compounds. Mot

than a decade ago phenobarbital was shown to enhance

the biliary excretion of BSP, DB 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, succi-
nylsulfath tion of several nonmetabolized organic compounds. More
than a decade ago phenobarbital was shown to enhance
the biliary excretion of BSP, DBSP, amaranth, succi-
nylsulfathiazole, chlorothiazide, and ouabain (620, 1045,
125 than a decade ago phenobarbital was shown to enhan
the biliary excretion of BSP, DBSP, amaranth, succ
nylsulfathiazole, chlorothiazide, and ouabain (620, 104
1255). More recently it has been demonstrated th
bromcresol gree anth, and iodoxamic acid (344) are also eliminated that debromcresol green, BSP-GSH (340, 341), eosine, amar-
anth, and iodoxamic acid (344) are also eliminated more The rapidly into the bile of barbiturate-pretreated rats 1255). More recently it has been demonstrated that
bromcresol green, BSP-GSH (340, 341), eosine, amar-
anth, and iodoxamic acid (344) are also eliminated more
rapidly into the bile of barbiturate-pretreated rats. The
bilia bromcresol green, BSP-GSH (340, 341), eosine, amar-
anth, 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 α and increase in excretion of 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 exc 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-hydroxyphenyltrimary excretion of neostignme and its two metabolites dis also stimulated in phenobarbital-treated rats (1111). is
However, the increase in excretion of the unchanged P
drug was greater than that of either 3-hydroxyphenyltr

acid (1236), hexachlorophene (653), and many other out" effect (620). Since the inducers do not enhance the chemicals. Administration of phenobarbital to children biliary excretion of all compounds such as rose bengal with D WATKINS
might be due to an increase in amount of carrier protein
(286) or to a stimulation in bile flow causing a "wash (286) or to a stimulation 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 D WATKINS
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 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 benga (286) or to a stimulation in bile flow causing a "wash" out" effect (620). Since the inducers do not enhance the more than one transport system for the excretion of liary excretion of all compounds such as rose bengal
66) and indocyanine green (344, 620), there might be
ore than one transport system for the excretion of
ogenous organic acids.
The mechanism for the increased biliary ex

(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 micr 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 in-
ducers is complex. For some chemicals th exogenous organic acids.
The mechanism for the increased biliary excretion of
drugs after administration of microsomal enzyme in-
ducers is complex. For some chemicals the difference in
rate of biotransformation is importa The mechanism for the increased biliary excretion of
drugs after administration of microsomal enzyme in-
ducers is complex. For some chemicals the difference in
rate of biotransformation is important, for others bile
flow drugs after administration of microsomal enzyme in-
ducers 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
p ducers 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 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. Obably the ability or number of transport cand one chemicals into the hepatocyte and into the spaye sending venobiotics, a combination of these faeded.
2. <i>Chlorotoxicants*. As noted earlier, 3-methyl rene is a microso

many xenobiotics, a combination of these factors is
needed.
2. Chlorotoxicants. As noted earlier, 3-methylcholan-
threne is a microsomal enzyme inducer which does not
enhance bile flow, hepatic uptake, or biliary excretion needed.

2. Chlorotoxicants. As noted earlier, 3-methylcholan-

threne is a microsomal enzyme inducer which does not

enhance bile flow, hepatic uptake, or biliary excretion

and in fact tends to decrease hepatic excretory 2. Chlorotoxicants. As noted earlier, 3-methylcholan-
threne 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
(2 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
spe (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-methylcholan-
threne induces heme proteins with a maximal absorbance of 44 (287, 619, 620). In contrast to the barbiturates
induce a family of isozymes that have an absorp
spectrum maximum at 450 nm (P-450), 3-methylch
threne induces heme proteins with a maximal absorb
of 448 nm (P-448). The chl induce a family of isozymes that have an absorption
spectrum maximum at 450 nm (P-450), 3-methylcholan
threne induces heme proteins with a maximal absorbanc
of 448 nm (P-448). The chlorotoxicants 2,3,7,8-tetra
chlorodibenz spectrum maximum at 450 nm (P-450), 3-methylcholan-
threne induces heme proteins with a maximal absorbance
of 448 nm (P-448). The chlorotoxicants 2,3,7,8-tetra-
chlorodibenzo-p-dioxin (TCDD), polychlorinated bi-
phenyls, p threne induces heme proteins with a maximal absorban
of 448 nm (P-448). The chlorotoxicants 2,3,7,8-tetr
chlorodibenzo-p-dioxin (TCDD), polychlorinated b
phenyls, polybrominated biphenyls, chlorodecone (K
pone), and mirex of 448 nm (P-448). The chlorotoxican
chlorodibenzo-p-dioxin (TCDD), polyophenyls, polyorominated biphenyls, chl
pone), and mirex are similar to 3-meth
and decrease hepatic excretory function.
TCDD pretreatment delays the p lorodibenzo-p-dioxin (TCDD), polychlorinated bi-
enyls, polybrominated biphenyls, chlorodecone (Ke-
ne), and mirex are similar to 3-methylcholanthrene
d decrease hepatic excretory function.
TCDD pretreatment delays the pla

phenyls, polybrominated biphenyls, chlorodecone (Ke-
pone), and mirex are similar to 3-methylcholanthrene
and decrease hepatic excretory function.
TCDD pretreatment delays the plasma disappearance
and biliary excretion of pone), 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) 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 biph TCDD pretreatment delays the plasma disappearane
and biliary excretion of ouabain and indocyanine gree
(456, 1062, 1063, 1287) but not BSP or DBSP (1287
The polychlorinated biphenyls are generally regarded a
microsomal enz 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 elimi-
nati (456, 1062, 1063, 1287) but not BSP or DBSP (1287).
The polychlorinated biphenyls are generally regarded as
microsomal enzyme inducers, but they impair the elimi-
nation of digitoxin by apparently decreasing the activity
 The polychlorinated biphenyls are generally regarded as
microsomal enzyme inducers, but they impair the elimi-
nation of digitoxin by apparently decreasing the activity
of the enzymes responsible for cleavage of the digito microsomal enzyme inducers, but they impair the and
nation of digitoxin by apparently decreasing the ac
of the enzymes responsible for cleavage of the digit
residues (1042). Mirex and Kepone reduce the b
excretion of imipr mation 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 phenolphthal of the enzymes responsible for cleavage of the digitoxose
residues (1042). Mirex and Kepone reduce the biliary
excretion of imipramine metabolites and phenolphthal-
ein glucuronide, but not of BSP, despite an increase in
b excretion of imipramine metabolites and phenolphthal-
ein glucuronide, but not of BSP, despite an increase in
bile flow (227, 785). Impaired biliary excretion probably
results from decreased transfer of metabolites into bi (785). n glucuronide, but not of BSP, despite an increase in
le flow (227, 785). Impaired biliary excretion probably
sults from decreased transfer of metabolites into bile
85).
The detrimental effects of the chlorotoxicants might many xenobiotics, a combination of these factors is
needed.
2. Chlorotoxicants. As noted earlier, 3-methylcholan-
threne is a microsomal enzyme inducer which does not
enhance bile flow, hepatic uptake, or biliary excretio

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 (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^+ATP ase and
 $Mg^{++}ATP$ ase (225, 226, 242, 786). The TCDD-induced
depress 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 pretreat-
ing rat 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 TC Mg⁺⁺-ATPase (225, 226, 242, 786). The TCDD-induced
depression of ouabain excretion was masked by pretreat-
ing rats with PCN or spironolactone on days 6 to 9 after
TCDD injection (914). Even though ouabain transport
into ing 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 ouabai 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).
Pe 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 retro-
d depressed suggesting that the carrier system for ouabain
is separate and distinct from the two ATPases (915).
Peterson (909) has suggested that TCDD causes retro-
differentiation to the neonatal state of hepatic gene
expre

PHARMACOLOGICAL REVIEWS

BILE FORMATION, HEPATIC UPT
adult TCDD-intoxicated (914) and control newborn rats
(637) with PCN produces expression of normal adult
levels of ouabain uptake and biliary excretion (456). BILE FORMATION, HEPATIC
adult TCDD-intoxicated (914) and control newborn re
(637) with PCN produces expression of normal ad
levels of ouabain uptake and biliary excretion (456).
3. Bile Acids. Intravenous infusions of bile

3. Bile Acids. Intravenous infusions of bile acids can 2644 (867), or ethacrynic acid (1210) do not enhance the increase the biliary excretion of BSP (106, 128, 313, 355, biliary excretion of BSP and/or DBSP.
422, 426, 678 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 (637) with PCN produces expression of normal adult the
levels of ouabain uptake and biliary excretion (456). tio
3. Bile Acids. Intravenous infusions of bile acids can
264
increase the biliary excretion of BSP (106, 128, levels of ouabain uptake and biliary excretion (456) . tion o
3. Bile Acids. Intravenous infusions of bile acids can
increase the biliary excretion of BSP (106, 128, 313, 355, biliary
422, 426, 678, 989), indocyanine gre 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), bili-
rubin (404, 632), DBSP (1211), and rose bengal (rubin (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). 422, 426, 678, 989), indocyanine green $(1211, 1218)$, bili-
rubin $(404, 632)$, DBSP (1211) , and rose bengal $(422, 66$ son
766). However, bile acid administration does not enhance of am
the biliary excretion of ouabai rubin (404, 632), DBSP (1211), and rot 766). However, bile acid administration do
the biliary excretion of ouabain or K-s
(795, 1216), eosine, BSP-GSH (422), eth
acetyl-PAEB, or d-tubocurarine (1213).
Bile acids probably e biliary excretion of ouabain or K-strophanthoside injustical probably even have a physiological role in mite acids probably even have a physiological role in mite biliary excretion of bilirubin. For example, it appears (79

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 excret (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 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 bili-

rubin Bile acids probably even have a physiological role
the biliary excretion of bilirubin. For example, it appea
that taurocholate is essential for normal exogenous bi
rubin excretion in ponies (300). More recent studi
indica cholate is essential for normal exogenous bili-
that taurocholate is essential for normal exogenous bili-
rubin excretion in ponies (300). More recent studies coindicate infusions of either chenodeoxycholate or tauro-
cho rubin excretion in ponies (300). More recent studies celundicate infusions of either chenodeoxycholate or tauro-
cholate (8 to 9 μ mol/min) increase bilirubin excretion here
60% to 80% following 5 hours of biliary diver malcate infusions of either chenodeoxycholate or tauro-
cholate (8 to 9 μ mol/min) increase bilirubin excretion he
60% to 80% following 5 hours of biliary diversion where
endogenous bile acid excretion equals the amount cholate (8 to 9 μ mol/min) increase bilirubin excretion hepatoc 60% to 80% following 5 hours of biliary diversion where and biliar endogenous bile acid excretion equals the amount being Acute synthesized (301). Infusion 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
 μ mol/min) after biliary diversion increases bile flow 4 ention spin and extremely quals the amount being
synthesized (301). Infusion of dehydrocholate (10.5 d
 μ mol/min) after biliary diversion increases bile flow 45% the
to 60% and excretion of bile acid 35% above the level mich and the micropology 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 o duce to hepatic synthesis. Emilyon secretion is not exchanged. These results suggest that bilirubin excretion tald
depends on the micelle-forming capacity of endogenous pa
bile acids. (1)
Cholestyramine-induced bile acid d

bile acids. (1)
bile acids. (1)
cholestyramine-induced bile acid depletion markedly
decreases the excretion of indocyanine green, BSP, rose
bengal, and bromcresol green (427). Biliary secretion of an
these anions is stimul decreases the excretion of indocyanine green, BSP, rose and biotransformation (1088) and is reduced in rats
bengal, and bromcresol green (427). Biliary secretion of anesthetized with diethyl ether (560). This may be due
th 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
ac 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 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
w 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 concentratio 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 (1211, 1216), 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
wer would decrease the enective 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
(12 excretion (1035, 1218, 1232). However, no differences
were observed in binding of organic anions to micelles
(1211), and non-micelle-forming dehydrocholate also in-
creases excretion of exogenous dyes (94, 1211). Other
stu were observed in binding of organic anions to micell (1211), and non-micelle-forming dehydrocholate also is creases excretion of exogenous dyes (94, 1211). Oth studies also suggest that complexation with biliary m celles i (1211), and non-micelle-forming dehydrocholate also i
creases excretion of exogenous dyes $(94, 1211)$. Oth
studies also suggest that complexation with biliary n
celles is not the only factor involved. Excretion of diet
y creases excretion of exogenous dyes (94, 1211). Oth
studies also suggest that complexation with biliary n
celles is not the only factor involved. Excretion of diet
ylstilbestrol was increased during taurocholate or tau
deh celles is not the only factor involved. Excretion of dieth-
ylstilbestrol was increased during taurocholate or tauro-
dehydrocholate infusions (820). Since diethylstilbestrol
monoglucuronide does not form micelles with tau monoglucuronide does not form micelles with taurode-
hydrocholate, micelle formation alone cannot explain the enzymes (324, 551, 957). However, a comprehensive
evidence for bile-flow-dependent, carrier-mediated study of th Muslimestrof was increased during tautocholate or tauro-
dehydrocholate infusions (820). Since diethylstilbestrol
monoglucuronide does not form micelles with taurode-
hydrocholate, micelle formation alone cannot explain th monoglucuronide does not form micelles with taurode-
hydrocholate, micelle formation alone cannot explain the
evidence for bile-flow-dependent, carrier-mediated
transport of the conjugate into bile. It is possible that
bil hydrocholate, micelle formation alone cannot explain the vidence for bile-flow-dependent, carrier-mediate transport of the conjugate into bile. It is possible the bile acids can facilitate anion transport by allosterintera 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 caus-
 transport of the conjugate into bile. It is possible that like acids can facilitate anion transport by allosteric interactions with canalicular membrane carriers or causing changes in membrane fluidity. Finally, interferen bile acids can facilitate anion transport by allosteric
interactions with canalicular membrane carriers or caus-
ing changes in membrane fluidity. Finally, interference
with storage within the hepatocyte may also influence g changes in membrane fluidity. Finally, interference of the storage within the hepatocyte may also influence of the storage within the hepatocyte may also influence of the storage the biliary excretion of numbiotics is no

ing changes in membrane ituatry. 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 ac

BILE FORMATION, HEPATIC UPTAKE, AND BILIARY EXCRETION 39
adult TCDD-intoxicated (914) and control newborn rats anine green but not for BSP (615). Not all compounds
(637) with PCN produces expression of normal adult that in AM AND BILIARY EXCRETION 39
Anine green but not for BSP (615). Not all compounds
that increase canalicular bile flow increase biliary excre-KE, AND BILIARY EXCRETION
anine green but not for BSP (615). Not all compount
that increase canalicular bile flow increase biliary excre-
tion of xenobiotics. For example, theophylline (70), S SUPER AND BILIARY EXCRETION 39

anine green but not for BSP (615). Not all compounds

that increase canalicular bile flow increase biliary excre-

tion of xenobiotics. For example, theophylline (70), SC-

2644 (867), or et anine green but not for BSP (615). Not all compounds
that increase canalicular bile flow increase biliary excre-
tion of xenobiotics. For example, theophylline (70), SC-
2644 (867), or ethacrynic acid (1210) do not enhance anine green but not for BSP (615). Not
that increase canalicular bile flow increa
tion of xenobiotics. For example, theoph
2644 (867), or ethacrynic acid (1210) do
biliary excretion of BSP and/or DBSP.
However, bile acids at increase canalicular bile flow increase biliary excrement of xenobiotics. For example, theophylline (70), SC-
44 (867), or ethacrynic acid (1210) do not enhance the
liary excretion of BSP and/or DBSP.
However, bile acid

tion 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 of some exogenous cholephils. For example, the excretion
of amaranth into bile was inhibited by simultaneous
injection of lithocholic, chenodeoxycholic, deoxycholic, 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 lithochol riowever, one actus can also depress the enfinitation
of some exogenous cholephils. For example, the excretion
of amaranth into bile was inhibited by simultaneous
injection of lithocholic, chenodeoxycholic, deoxycholic,
ch 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
m (796). olic, and dehydrocholic acids (430). The inhibitory
fect of lithocholic acid may be due to toxic actions on
itochondrial respiration (430) or ATPase function
96).
4. *Hepatotoxicants*. Chemicals that are toxic to liver
Ils

effect of infoculous acid may be due to toxic actions of
mitochondrial respiration (430) or ATPase function
(796).
4. Hepatotoxicants. Chemicals that are toxic to live
cells can affect biliary excretion in several ways. To mixedionular respiration (450) or Arrase function
(796).
4. Hepatotoxicants. Chemicals that are toxic to liver
cells can affect heliary excretion in several ways. Toxi-
cants can affect hepatic blood flow, uptake into the
 4. Hepatotoxicants. Chemicals that are toxic to live
cells can affect biliary excretion in several ways. Toxicants can affect hepatic blood flow, uptake into the
hepatocyte, biotransformation and storage, excretion
and bil 4. *Hepatotoxicanis*. Chen
cells can affect biliary excr
cants can affect hepatic b
hepatocyte, biotransformat
and biliary tract permeabilit
Acute treatment with ca cents can ariect binary 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

hepatocyte, biotransformation and storage, excretion,
and biliary tract permeability.
Acute treatment with carbon tetrachloride markedly
decreases the biliary excretion of BSP (661, 947). Fur-
thermore, rats chronically in and binary tract permeability.

Acute treatment with carbon tetrachloride markedly

decreases the biliary excretion of BSP (661, 947). Fur-

thermore, rats chronically intoxicated with carbon tet-

rachloride have a delaye Acute treatment with carbon tetrachloride markedly
decreases the biliary excretion of BSP (661, 947). Fur-
thermore, rats chronically intoxicated with carbon tet-
rachloride have a delayed plasma clearance and biliary
excr decreases the biliary excretion of BSP (661, 947). Fur-
thermore, rats chronically intoxicated with carbon tet-
rachloride have a delayed plasma clearance and biliary
excretion of indocyanine green (530). Intrahepatic me-
 thermore, rats chronically intoxicated with carbon tet-
rachloride have a delayed plasma clearance and biliary
excretion of indocyanine green (530). Intrahepatic me-
tabolism and/or transport into bile of BSP is also im-
p racmorae
excretion of
tabolism an
paired after
(171, 172).
Biliary ex cretion of indocyanine green (530). Intrahepatic me-
bolism and/or transport into bile of BSP is also im-
ired after styrene- or styrene oxide-induced liver injury
71, 172).
Biliary excretion of acetaminophen depends on do

tabolism and/or transport into bile of BSP is also im-
paired after styrene- or styrene oxide-induced liver injury
(171, 172).
Biliary excretion of acetaminophen depends on dose
and biotransformation (1088) and is reduced paired 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 (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 Ether depends on does
and biotransformation (1088) and is reduced in rata
anesthetized with diethyl ether (560). This may be due
to decreased conjugation with glucuronic acid since di
ethyl ether depletes hepatic UDP-glucu and biotraisionmation (1000) and is reduced in rats

anesthetized with diethyl ether (560). This may be due

to decreased conjugation with glucuronic acid since di-

ethyl ether depletes hepatic UDP-glucuronic acid con-
 the decreased conjugation with giactronic acid since unter-
ethyl ether depletes hepatic UDP-glucuronic acid con-
centration (303, 1238, 1239). Pretreatment of rats with
galactosamine and borneol, which also deplete UDPGA
 ethyl ether depletes hepatic ODF-glucturoffic actu con-
centration (303, 1238, 1239). Pretreatment of rats with
galactosamine and borneol, which also deplete UDPGA
(1236). Excretion of acetaminophen-GSH conjugate may
be re cells can affect biliary excretion in several ways. Toxical
cants can affect hepatic blood flow, uptake into the hepatocyte, biotransformation and storage, excretion,
and biliary tract permeability.
Acute treatment with c 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 suppres (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 r 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 oxid suppression of hepatic GSH synthesis (716). Perfusion suppression of hepatic GSH synthesis (710). Ferfusion
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 hepatic GSH concentration with a concomitant increase
in oxidized GSH excretion into bile (414). Chemical
induced loss of microsomal metabolizing systems ha
been reviewed (241). Thus, numerous data indicate he
patotoxicant oxidized GSH excretion into bile (414). Chemical-
duced loss of microsomal metabolizing systems has
en reviewed (241). Thus, numerous data indicate he-
totoxicants can markedly alter xenobiotic metabolism.
Several studies been reviewed (241). Thus, numerous data indicate hepatotoxicants can markedly alter xenobiotic metabolism.
Several studies have attempted to demonstrate liver patotoxicants can markedly alter xenobiotic metabolism.

patotoxicants can markedly alter xenobiotic metabolism
Several studies have attempted to demonstrate live
lobule heterogeneity with respect to drug-metabolizing
enzymes (324, 551, 957). However, a comprehensive
study of th Several studies have attempted to demonstrate live
lobule heterogeneity with respect to drug-metabolizir
enzymes $(324, 551, 957)$. However, a comprehensive
study of the effects of seven hepatotoxicants (allyl alce
hol, a chologie meterogeneity with respect to trug-metabonizing
enzymes (324, 551, 957). However, a comprehensive
study of the effects of seven hepatotoxicants (allyl alco-
hol, aflatoxin B₁, ANIT, bromobenzene, carbon tetra-
c study of the effects of seven hepatotoxicants (allyl alcohol, aflatoxin B₁, ANIT, bromobenzene, carbon tetra-
chloride, 1,1-dichloroethylene, cadmium chloride) indi-
cates that poisoning seriously affects the microsomal
 hol, aflatoxin B₁, ANIT, bromobenzene, carbon tetra-
chloride, 1,1-dichloroethylene, cadmium chloride) indi-
cates that poisoning seriously affects the microsomal
oxidases without significantly influencing the activities choride, 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 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
lob 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
lob

aspet

PHARMACOLOGICAL REVIEW!

spet

 $\overline{\mathbb{O}}$

40 KLAASSEN AND WATKINS
activity after chemically induced necrosis of a specific ated metaboli
region of the hepatic lobule (432). In vivo metabolism of ing time (539 KLAASSEN AND
activity after chemically induced necrosis of a specific
region of the hepatic lobule (432). In vivo metabolism of
intervals of aminopyrine was not affected by regio-select-
ive damage by bromobenzene or allyl activity after chemically induced necrosis of a spec
region of the hepatic lobule (432). In vivo metabolism
ethanol or aminopyrine was not affected by regio-sele
ive damage by bromobenzene or allyl alcohol (1269).
After ex Evity after chemically moded necrosis of a specion of the hepatic lobule (432). In vivo metabolis
hanol or aminopyrine was not affected by regio-se
e damage by bromobenzene or allyl alcohol (1269)
After exposure to bromobe

region of the hepatic lobule (432). In vivo metabolism of
ethanol or aminopyrine was not affected by regio-select-
ive damage by bromobenzene or allyl alcohol (1269).
After exposure to bromobenzene or carbon tetrachlo-
rid ive damage by bromobenzene or allyl alcohol (1269).
After exposure to bromobenzene or carbon tetrachlo-
ride, centrilobular hepatocytes contributed to the re-
moval of 13% to 18% of a physiological load of taurocho-
late. Filter exposure to bromobenzene or carbon tetracino-
ride, centrilobular hepatocytes contributed to the re-
moval of 13% to 18% of a physiological load of taurocho-
late. The 50% decrease in bile flow after bromobenzene
su moval of 13% to 18% of a physiological load of taurocholate. The 50% decrease in bile flow after bromobenzene
late. The 50% decrease in bile flow after bromobenzene
suggests that damage to the centrilobular region produce moval of 13% to 18% of a physiological foat of tatrocholate. The 50% decrease in bile flow after bromobenzen suggests that damage to the centrilobular region produce alterations in bile production and that 13% to 18% ate: The 50% decrease in the how after bromood
suggests that damage to the centrilobular region pr
alterations in bile production and that 13% to 1
physiological bile acids reach bile via centrilobula
atocytes (443). Penta suggests that damage ω the centrificious region produces 13
alterations in bile production and that 13% to 18% of ste
physiological bile acids reach bile via centrilobular hep-
atocytes (443). Pentachlorophenol and 2,4 atterations in one production and that 13% to 16% or
physiological bile acids reach bile via centrilobular hep-
atocytes (443). Pentachlorophenol and 2,4,6-trichloro-
other phenol inhibit the excretion of BSP into t 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 aucytes (443). Fentachlorophenol and 2,4,0-trichior
phenol inhibit the excretion of BSP into the medium isolated liver cells (406). Impaired BSP transport ma
be due to depressed energy production since both pheno
uncouple phenor minut the excretion of BSF into the medium by
isolated liver cells (406) . Impaired BSP transport may
be due to depressed energy production since both phenol
uncouple oxidative phosphorylation in hepatocellula
mit isolated liver cells (406). Impaired BSP transport may
be due to depressed energy production since both phenols
into
uncouple oxidative phosphorylation in hepatocellular
in finitochondria. Although acute administration of be due to depressed energy production since both phenois
uncouple oxidative phosphorylation in hepatocellulai
mitochondria. Although acute administration of afla-
toxin B_1 decreases bile flow (1193), excretion of BSP i mitochondria. Although acute administration of a
toxin B_1 decreases bile flow (1193), excretion of BSP
bile is not seriously diminished (165). In contrast, to
rolithocholate-induced reduction in bile flow sign
cantly d miochondria. Although acute administration of ana-
toxin B_1 decreases bile flow (1193), excretion of BSP in
bile is not seriously diminished (165). In contrast, tau-
rolithocholate-induced reduction in bile flow signif the is not senously diminished (105). In contrast, tau-
rolithocholate-induced reduction in bile flow signifi-
cantly decreases the secretion of adriamycin into bile,
and the data suggest that the disposition of this chemo Follocholate-induced reduction in the how significantly decreases the secretion of adriamycin into bile, and the data suggest that the disposition of this chemo-
therapeutic agent depends on the rate of bile production (11 called the data suggest that the disposition of this chemo-
therapeutic agent depends on the rate of bile production
(1163). A toxic metabolite of ticrynafen reportedly re-
duces bile flow and BSP excretion, but the mecha is not known (1299). Administration of an extract of the production

(1163). A toxic metabolite of ticrynafen reportedly re-

duces bile flow and BSP excretion, but the mechanism

is not known (1299). Administration of an (1103). A toxic metabolite of the profection, but the mechanism
is not known (1299). Administration of an extract of
Amanita phalloides significantly increases the permea-
bility of the biliary tree as evidenced by the duces one now and BSF excretion, but the mechanism
is not known (1299). Administration of an extract of
Amanita phalloides significantly increases the permea-
bility of the biliary tree as evidenced by the reduction in
r 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 bility of the binary 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 tra

deleterious effect on hepatic excretory function.

S. Liver Injury. Injury to the liver generally produces

deleterious effects on hepatic excretory function. The

jaundice following liver injury results from decreased ti jaundice chemicals can arect one now, xendonouc transport,
and biliary tree permeability.
5. Liver Injury. Injury to the liver generally produces
deleterious effects on hepatic excretory function. The
jaundice following li and binary 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 f bile. Dye clearance techniques deletermine the 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 disease of hepatic excrement interestion. 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 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
disease or chemical-induced liver injury on the plasma
d removal of bilirubin from plasma and its excretion in bile. Dye clearance techniques determine the effect disease or chemical-induced liver injury on the plass disappearance and biliary excretion of cholephilic dy (BSP and one. 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 choles-
 disappearance and biliary excretion of cholephili
disappearance and biliary excretion of cholephili
(BSP and indocyanine green). Liver injury of the c
tatic type usually decreases bilirubin excretion
greater extent than do Seppearance and binary excretion of cholephinc dyes
SP and indocyanine green). Liver injury of the choles-
tic type usually decreases bilirubin excretion to a
eater extent than does parenchymal cell injury.
Several studie

(BSF and mootyannie green). Liver injury of the tholes-
tatic type usually decreases bilirubin excretion to a
greater extent than does parenchymal cell injury.
Several studies have evaluated the effect of liver injury
on Example of the discussed burntum extretion 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 Several studies have evaluated the effect of liver injury of $(626, 627, 635, 1065)$. Results show marked differences ish in the effect of bile duct ligation on the LD50 of 20 ton xenobiotics (626). An extensive study of 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 2 on the toxicity of chemicals hormany excreted mot one
 $(626, 627, 635, 1065)$. Results show marked differences ish

in the effect of bile duct ligation on the LD50 of 20 ton

xenobiotics (626). An extensive study of 175 (020, 027, 035, 1005). Results show marked differences $\frac{1}{2}$ in the effect of bile duct ligation on the LD50 of 20 ton xenobiotics (626). An extensive study of 175 chemicals indicated that ligation of the common bile In the enect of the duct ingation 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 mulcated that inguiton of the common bile duct and $\frac{1}{2}$
partial hepatectomy increase the adverse effects of 39 h
and 53 drugs, respectively (1065). The mechanism for b
increased toxicity after ligation of the bile du partial hepatecomly increase the adverse effects of 33 held
and 53 drugs, respectively (1065). The mechanism for bil
increased toxicity after ligation of the bile duct is unclear rat
and does not necessarily relate to the and 53 drugs, respectively (1065). The mechanism for biliary excretion of the above four drugs and bile flow
increased toxicity after ligation of the bile duct is unclear rate were 60% to 65% and 80% to 90% of increased witchy after figation of the bile duct is uncleared and does not necessarily relate to the percentage of compound normally excreted into bile. For example, BSI is excreted almost exclusively via the bile, but its

D WATKINS
ated metabolite are increased prolonging ketamine slee
ing time (539). If toxicity relates to the peak concentr D WATKINS
ated metabolite are increased prolonging ketamine s
ing time (539). If toxicity relates to the peak concention in blood, bile duct ligation would probably have D WATKINS
ated metabolite are increased prolonging ketamine sleep-
ing time (539). If toxicity relates to the peak concentra-
tion in blood, bile duct ligation would probably have no
effect. However, if toxicity relates to ated metabolite are increased prolonging ketamine sleep-
ing time (539). If toxicity relates to the peak concentra-
tion in blood, bile duct ligation would probably have no
effect. However, if toxicity relates to persisten ated metabolice are increased prolonging setamme sieep-
ing time (539). If toxicity relates to the peak concentra-
tion in blood, bile duct ligation would probably have no
effect. However, if toxicity relates to persistenc have marked effects. Further work is needed to test this hypothesis.
The marked blood levels, then ligation would be expected to have marked effects. Further work is needed to test this hypothesis. hypothesis. exter. However, in toxicity relates to persistence of elected blood levels, then ligation would be expected to twe marked effects. Further work is needed to test this pothesis.
Bile duct ligation increases diethylstilbestr

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 bilia steries. These 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 i Bile duct ligation increases diethylstilbestrol toxicial 130-fold and decreases the plasma disappearance of the steroid (627). These data indicate biliary excretion is the primary excretory pathway for diethylstilbestrol. Due duct ngation increases diethylistinestich toxicity
130-fold and decreases the plasma disappearance of this
steroid (627). These data indicate biliary excretion is the
primary excretory pathway for diethylstilbestrol. A some drugs to a greater extent than others is that there could be compensatory shifts to excrete these chemicals of why ligation increases toxicity of some drugs to a greater extent than others is that there could be compe 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 i primary exercity pathway for diethylsthestiol. And other hypothesis of why ligation increases toxicity of some drugs to a greater extent than others is that the could be compensatory shifts to excrete these chemical into u 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 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 biliary route (68). Biliary excretion of melphalan is en-
hanced by ligating the renal arteries (151) indicating the
interrelationship of biliary and renal excretion. Similar in fact, increased drinary emimiation of one actd sunates
in hamsters is observed after decreased excretion by the
biliary route (68). Biliary excretion of melphalan is en-
hanced by ligating the renal arteries (151) indic alterations of xenobiotic excretion for melphalan is enhanced by ligating the renal arteries (151) indicating the interrelationship of biliary and renal excretion. Similar alterations of xenobiotic excretion have been not mateur by ngabing the tends above. They indicating the
interrelationship of biliary and renal excretion. Similar
alterations of xenobiotic excretion have been noted after
reduced renal or hepatic function produced by potas dericationship of ontary and tenat excretion. Shimal
terations of xenobiotic excretion have been noted after
duced renal or hepatic function produced by potassium
chromate and carbon tetrachloride, respectively (231).
Bile 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). Elilary are terior of melp

reduced renal or hepatic function mave been noted and and
dichromate and carbon tetrachloride, respectively (231).
Bile duct ligation reduces the plasma clearance of
pentobarbital and meperidine by apparently altering the 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 i distributed and canonical certactionide, respectively (201).
Bile duct ligation reduces the plasma clearance of
pentobarbital and meperidine by apparently altering the
initial volume of distribution. A significant reductio pericolation. A significant reduction in
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. motal 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 extractio periusate flow was observed in isolated periused fiver
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
b Experiments with organs from rats with prev
duct ligation. Reduced clearance of both a high ex
drug and a lower extraction drug suggest both
blood flow and drug-metabolizing activity may b
by extrahepatic biliary tract obs The matter is a lower extraction drug suggest both hep
ood flow and drug-metabolizing activity may be alternated the extrahepatic biliary tract obstruction (675).
Two-thirds hepatectomy or selective biliary obstruction
on

ting and a lower extraction didg suggest both help
blood flow and drug-metabolizing activity may be alt
by extrahepatic biliary tract obstruction (675).
Two-thirds hepatectomy or selective biliary obs
tion and bile duct li by extrahepatic biliary tract obstruction (675).
by extrahepatic biliary tract obstruction (675).
Two-thirds hepatectomy or selective biliary obstruc-
tion and bile duct ligation affect the plasma disappear-
ance of xenobi by extranspact of mary tract obstruction (675).

Two-thirds hepatectomy or selective biliary obstruction

tion and bile duct ligation affect the plasma disappear-

ance of xenobiotics differently (635). Ligation decreased Two-timus hepatectomy of selective binary 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 ex dom and one duct ngation ariest the plasma disappear
ance of xenobiotics differently (635). Ligation decreased
the elimination of BSP and indocyanine green to a
greater extent than did partial hepatectomy, while tha
of PAE ance of aenoblocks differently (055). Eigation 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 he greater extent than the 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 inter-
ruptio of PAEB and ouabant was decreased more after two-
thirds hepatectomy. The data indicate that clearance of
BSP and indocyanine green is more sensitive to inter-
ruption of transfer from liver to bile, while elimination
of P explored in the data matches that clearance
BSP and indocyanine green is more sensitive to int
ruption of transfer from liver to bile, while eliminat
of PAEB and ouabain is more dependent upon hepe
mass. Hepatic excretion Bot and mootyanine green is more sensitive to m
ruption of transfer from liver to bile, while elimina
of PAEB and ouabain is more dependent upon hep
mass. Hepatic excretion of hexachlorophene was din
ished by both bile duc topoon of transier from fiver to the, while emininate of PAEB and ouabain is more dependent upon hep mass. Hepatic excretion of hexachlorophene was din ished by both bile duct ligation and two-thirds hepatomy and its toxic 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 compo

fished 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 hepatectomize held by both bile duct ligation and two-thrids hepatectomy and its toxicity was markedly increased (653).
There appears to be a reserve capacity to excrete
foreign compounds. Even though livers from partia
hepatectomized r 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 w There appears ω be a reserve capacity ω 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 wer college 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 (63 meparectomized 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 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
a rate were 60% to 65% and 80% to 90% of that of th
controls (635). Further evidence of this reserve capacit
was the observation of a 13-fold increase in serum bi
acids 48 hours after selective biliary obstruction, an
that s that secretion of water, bile acids, cholesterol, and phos-
pholipids by the nonobstructed lobes was similar to controls (14). This reserve capacity can be stimulated by increased substrate concentrations (14, 1092, 1235).

BILE FORMATION, HEPATIC UPTAKE

trols (14). This reserve capacity can be stimulated by cret

increased substrate concentrations (14, 1092, 1235). bec

Bile duct ligation 24 hours before administration of a dru

lethal dose 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
 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 inc increased substrate concentrations (14, 1092, 1230).

Bile duct ligation 24 hours before administration of a

lethal dose of an extract of Amanita phalloides protects

cirats from lethality and prevents a toxin-induced inc Find 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 obs rats from lethanty and prevents a toxin-modeed 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
a In binary tree permeability (372). An increase in bile with the dividend after bile duct ligation. The mechanism for protection in against phallotoxins by ligation is unclear but may result the from increases in bile acid 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 f Studies of the mechanism of postcholestatic cholensis (10) of the mechanism of postcholestatic choleresis cholestatic of the mechanism of postcholestatic choleresis the biliary obstruction indicate canalicular permeabil-

biliary obstruction with the actual to binding sites (510) application indicate can duct ligated rats (1228).
Studies of the mechanism of postcholestatic chole after biliary obstruction indicate can alicular permetity to (12). Studies of the mechanism of postcholestatic choleresis after biliary obstruction indicate canalicular permeability to inulin and Na^+K^+ATP ase activity are increased (10). Canalicular permeability is greater after a after biliary obstruction indicate canalicular permeabil-
ity to inulin and Na^+K^+ATP ase activity are increased
(10). Canalicular permeability is greater after adminis-
tration of estrogens, phalloidin, taurolithocholat solvent flow across tight junctions and the canalicular
tration of estrogens, phalloidin, taurolithocholate, and
chlorpromazine (268, 352, 1149). These data indicate net
solvent flow across tight junctions and the canalicu cration of estrogens, phanologin, tauronthocholate, and
chlorpromazine (268, 352, 1149). These data indicate net
solvent flow across tight junctions and the canalicular
membrane, suggesting canalicular flow does not depend chorpromazine (208, 302, 1149). These data mulcate his
solvent flow across tight junctions and the canalicula
membrane, suggesting canalicular flow does not depen
primarily on the leakiness of these barriers. This is
creas solvent how across ught junctions and the canantular
membrane, suggesting canalicular flow does not depend
primarily on the leakiness of these barriers. This in-
creased permeability is not a typical response of drug-
indu 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 c lestasis (326). Moreover, the emianced Na -

K⁺-ATPase activity in livers from 3-day cholestatic rats

correlates with the postobstructive choleresis (10). The

lestasis which suggests an adaptive response of the

ATPase rrelates with the postobstructive choleresis (10). The patic content of this enzyme increases during cho-
tasis which suggests an adaptive response of the
TPase to complete biliary obstruction.
Liver regeneration has been

hepatic content of this enzyme increases during cho-
lestasis which suggests an adaptive response of the
ATPase to complete biliary obstruction.
Liver regeneration has been studied following partial
hepatectomy (722). Appa Estass which suggests an adaptive response of the F
ATPase to complete biliary obstruction.
Liver regeneration has been studied following partial
hepatectomy (722). Apparently there is an adaptive reg-
ulation involving de A IT asse to complete binary obstruction.
Liver regeneration has been studied following partia
hepatectomy (722). Apparently there is an adaptive reg
ulation involving derepression by low concentrations o
solutes and also Eiver regeneration has been statuted following partial
hepatectomy (722). Apparently there is an adaptive reg-
ulation involving derepression by low concentrations of
solutes and also hormonal changes. Specifically, in he mepatetionly (122). Apparently there is an adaptive
ulation involving derepression by low concentratio
solutes and also hormonal changes. Specifically, in
atocytes isolated from 70% hepatectomized rats,
was an increase in solutes and also hormonal changes. Specifically, in hepatocytes isolated from 70% hepatectomized rats, there was an increase in both influx and efflux of α -aminoiso-butyric acid. The amino acid transport system was Na solutes and also hormonal changes. Specifically, in
atocytes isolated from 70% hepatectomized rats, t
was an increase in both influx and efflux of α -amino
butyric acid. The amino acid transport system was l
dependent an atocytes isolated from 70% hepatectomized rats, then was an increase in both influx and efflux of α -aminoisolutyric acid. The amino acid transport system was Na dependent and energized partly by cationic transment bran was an increase in both initia and entux of α -aminoiso-
butyric acid. The amino acid transport system was Na⁺-
dependent and energized partly by cationic transmem-
brane gradients. The rapid emergence of this high af dependent and energized partly by cationic transmen
brane gradients. The rapid emergence of this high affility carrier system in the liver remnant following parti
hepatectomy may be important in the regulation of liver
reg brane gradients. The rapid em
ity carrier system in the liver
hepatectomy may be importan
regeneration after injury and
biotic clearance and excretion.
The effect of experimental he r carrier system in the liver remnant following partial
patectomy may be important in the regulation of liver
generation after injury and the maintenance of xeno-
tio clearance and excretion.
The effect of experimental he regeneration after injury and the maintenance of xeno-
biotic 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 The effect of experimental hepatobiliary injury on drug
metabolism was studied by using two surgical (selective $\frac{1}{2}$
and complete biliary obstruction) and two drug-induced $\frac{1}{2}$
(ethinylestradiol and ANIT) models I he enect of experimental nepatoonlary injury on dimetabolism was studied by using two surgical (select and complete biliary obstruction) and two drug-induction (ethinylestradiol and ANIT) models. Mild injury induction by 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 adm (ethinylestration and ANTT) models. While injury induce
by either selective obstruction or ethinylestradiol admin-
istration did not appreciably affect ¹⁴C-aminopyrin-
elimination by ¹⁴CO₂ breath analysis or the max by either selective obstruction or ethinylestradiol administration did not appreciably affect ¹⁴C-aminopyrine elimination by ¹⁴CO₂ breath analysis or the maximal velocity of demethylation. Severe injury caused by co istration did not appreciably affect ¹⁴C-aminopyrine physiolonelimination by ¹⁴CO₂ breath analysis or the maximal acids as velocity of demethylation. Severe injury caused by com-
plete obstruction and ANIT decreased (1268). Hepatobiliary function. Severe injury caused by com-
the obstruction and ANIT decreased $^{14}CO_2$ elimination
% and 60%, respectively, and demethylation by 35%
268).
Hepatobiliary function is compromised in several dis-
s

expectively, and demethylation by 35% and 60%, respectively, and demethylation by 35% here (1268).

Hepatobiliary function is compromised in several dis-

ease states. The total clearance of numerous drugs is cireduced in Hepatobiliary function is compromised in several disease states. The total clearance of numerous drugs is reduced in patients with cirrhosis (22, 109). Biliary ex-

BILE FORMATION, HEPATIC UPTAKE, AND BILIARY EXCRETION 41
apacity can be stimulated by cretion of *d*-propranolol is reduced in cirrhotic patients phanolal update is immoted in cents isolated from one
duct ligated rats (1228).
Studies of the mechanism of postcholestatic choleresis
after biliary obstruction indicate canalicular permeabil-
ity to inulin and Na⁺-K⁺ creased permeability is not a typical response of drug-
increased clearance after oral administration presumably
induced cholestasis (928). Moreover, the enhanced Na^+ -
 K^+ -ATPase activity in livers from 3-day cholesta AKE, AND BILIARY EXCRETION 41

cretion of d-propranolol is reduced in cirrhotic patients

because of an impaired ability of the liver to extract the AKE, AND BILIARY EXCRETION 41

cretion 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 AKE, AND BILIARY EXCRETION 41
cretion 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 ha cretion 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 concentrati cretion 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 concentrati 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
w 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
bil entriful patients have increased serian 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 occu with chronic liver disease have a decreased clearance of bile acids (299). Excessive accumulation of copper occurs what emonic nver discusse have a decreased clearance of the acids (299). Excessive accumulation of copper occum
in livers of patients with primary cirrhosis (1029). Although bile acid excretion is decreased, that of copper one actus (2007). Excessive accumulation of copper occurs
in livers of patients with primary cirrhosis (1029). Al-
though bile acid excretion is decreased, that of copper
was unaffected; this suggests that elevated copper though 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 was unaffected, this suggests that elevated copper con-

extrations do not occur as a result of decreased biliary

extretion of the metal. Administration of the chelating

agent, D-penicillamine, reduces the levels of cop the 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 statution of the metal. Rummisstatuton of the encated agent, D-penicillamine, reduces the levels of copper athe excretion of bile acids increases toward normal rad The mechanism for this effect is not known. In anot study, strated reduced storagement of porphyrin metabolism
strated reduced storage and elimination of BSP. Effects
may be related to derangement of porphyrin metabolism The mechanism for this effect is not known. In another
study, patients with porphyria cutanea tarda demon-
strated reduced storage and elimination of BSP. Effects
may be related to derangement of porphyrin metabolism
as co File incriming for this create is not anown. In another
study, patients with porphyria cutanea tarda demon-
strated reduced storage and elimination of BSP. Effects
may be related to derangement of porphyrin metabolism
as c strated reduced storage and elimination of BSP. Effects
may be related to derangement of porphyrin metabolism
as coproporphyrin may compete with BSP for binding to strated 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
bio increased clearance after oral administration presumably
igandin and for excretion (302). In smokers, systemic
bioavailability of lidocaine is decreased secondarily to an
increased clearance after oral administration presu 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 presuma bioavailability of lidocaine is decreased secondarily to an bioavailability of lidocaine is decreased secondarily to
increased clearance after oral administration presuma
reflecting induction of drug-metabolizing enzymes (51
In contrast, oral and systemic clearances of lidocaine
in increased creatures area can duminimated prosumes.

Feflecting induction of drug-metabolizing enzymes (515).

In contrast, oral and systemic clearances of lidocaine are

increased in patients with chronic hepatitis B. Admi Fenetung matched of drug-metabolizing enzymes (in contrast, oral and systemic clearances of lidocain increased in patients with chronic hepatitis B. Ad istration of perhexiline maleate induces liver injurgatients (937) and In contrast, oral and systemic clearances of lidocaine are
increased in patients with chronic hepatitis B. Admin-
istration of perhexiline maleate induces liver injury in
patients (937) and in rats (494) which can be chara 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. Ad istration of perhexiline maleate induces liver injury in
patients (937) and in rats (494) which can be character-
ized by an impairment of the transport maximum of
BSP. Additional information on the effect of liver disease patients (937) and in rats (494) which can be character-
ized 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,
 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

d liver injury has also been discussed (854).

VIII. Enterohepatic Circulation

Numerous chemicals are secreted into bile, deposited

to the intestinal lumen, reabsorbed by the intestine 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 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 topogr Numerous chemicals are secreted into bile, deposite
into the intestinal lumen, reabsorbed by the intestin
into the portal blood, and taken up by hepatocytes. The
process is limited topographically to the liver and inte
tin Trumerous chemicals are secreted mot one, 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 intesinto the portal blood, and taken up by hepatocytes. This
process is limited topographically to the liver and intes-
tine and is aptly called the enterohepatic circulation (fig.
7). This process enables living organisms to tine 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 estr 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 c $\sum_{i=1}^{n}$ 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 m D₃ and D₁₂, folic acid, pyridoxine, and estogens. Drugs
also undergo enterohepatic cycling and include cardiac
glycosides, chlorpromazine, indomethacin, antibiotics,
cholephilic dyes, and biliary contrast media. The mo 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 ileocyt cholephilic dyes, and biliary contrast media. The m
physiologically important of these chemicals is the k
acids as their transport out of hepatocytes and ileocy
into bile and portal blood, respectively, is a major driv
for physiologically important of these chemicals is the bile
acids as their transport out of hepatocytes and ileocyte
into bile and portal blood, respectively, is a major driving
force for solute and water movement within the 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 entero-
hepatic circulation. The degree of cycling of ot into bile and portal blood, respectively, is a major driving
force for solute and water movement within the entero-
hepatic circulation. The degree of cycling of other lipo-
philic and hydrophilic xenobiotics depends on bi force for solute and water movement within the entero-
hepatic circulation. The degree of cycling of other lipo-
philic and hydrophilic xenobiotics depends on bile acid
movement. Additional information on the enterohepatic hepatic circulation. The degree of cycling of oth
philic and hydrophilic xenobiotics depends on b
movement. Additional information on the enterc
circulation may be obtained in numerous reviev
260, 497, 498, 640, 648, 926,

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In the seventeenth century, Giovanni Borelli calcu-
In the seventeenth century, Giovanni Borelli calcu-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 A. Bile Acids
ioni in the seventeenth century, Giovanni Borelli calculated
lated that the total amount of bile entering the intestine
was substantially greater than the quantity present in the
the biliary tract. In 1759, The biliary of the sevent 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, Ed 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 Ba 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 was substantially greater than the quantity present
the biliary tract. In 1759, the Irish physician, Edwa
Barry suggested bile was reabsorbed by the intestin
and returned to the liver. This prescient idea of enter
hepatic 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 entero-
hepatic cycling of bile acids was strengthened by disc Barry suggested bile was reabsorbed by the intestines and returned to the liver. This prescient idea of entero-
hepatic cycling of bile acids was strengthened by discovery of the bile acids in 1809 by Berzelius and their
 hepatic 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 ery of the bile acids in 1809 by Berzenus 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 isotop 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 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 e 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 chole 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 pool escapes intestinal reabsorption and is excreted in
the feces (92) but endogenous synthesis from cholesterol
generally equals this loss. However, details of the ho-
meostatic mechanisms controlling synthesis, pool size 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, an generally equals this loss. However, det
meostatic mechanisms controlling synth
turnover frequency, bacterial metabolism,
bile acid secretion rates in health and
viewed but are poorly understood (160).
The driving forces o eostatic mechanisms controlling synthesis, pool size,

rnover frequency, bacterial metabolism, fecal loss, and

le acid secretion rates in health and disease are re-

wed but are poorly understood (160).

The driving force

turnover frequency, bacterial metabolism, fecal loss, and
bile acid secretion rates in health and disease are re-
viewed but are poorly understood (160).
The driving forces of the enterohepatic circulation port
include bil 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, i viewed but are poorly understood (160).

The driving forces of the enterohepatic circulation P

include bile acid secretion, concentration and storage in

the gallbladder, intestinal absorption, transport in portal

ven The driving forces of the enterohepatic circulation point include bile acid secretion, concentration and storage in the gallbladder, intestinal absorption, transport in portal and venous blood, and hepatic uptake. Active e the gallbladder, intestinal absorption, transport in portal
the gallbladder, intestinal absorption, transport in portal
venous blood, and hepatic uptake. Active excretion of
bile acids across the canalicular membrane into venous blood, and hepatic uptake. Active excretion of
bile acids across the canalicular membrane into bile is
the primary metabolic pump for the enterohepatic cir-
culation. This is the rate-limiting step in the transfer o bile acids across the canalicular membrane into bile is
the primary metabolic pump for the enterohepatic cir-
culation. This is the rate-limiting step in the transfer of
bile acids from blood or de novo synthesis into bile 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 con culation. I has as the rate-inmiting step in the transier 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 nese forces within the biliary tree result in continuous oduction of 0.8 to 1.0 l of bile per day in intact man
owever, flow fluctuates greatly and is reduced at night
d stimulated with feeding.
In species with a gallbladd 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 activ

However, now incruates greatry and is reduced at hight
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 movemen In species with a gallbladder, bile is concentrated live-
to 10-fold by active absorption of sodium and chloride
ions with passive movement of water (254). In response durin
to cephalic and hormonal influences during eatin

D WATKINS
(319, 1113). Thus, the gallbladder is a storage organ and
a mechanical pump in the enterohepatic circulation. D WATKINS
(319, 1113). Thus, the gallbladder is a storage organ
a mechanical pump in the enterohepatic circulation.
Bile acids are absorbed passively from all of the

WATKINS
19, 1113). Thus, the gallbladder is a storage organ and
mechanical pump in the enterohepatic circulation.
Bile acids are absorbed passively from all of the gas-
pintestinal tract via ionic and non-ionic diffusion ((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 gas-
trointestinal tract via ionic and non-ionic diffusion (25 a mechanical pump in the enteromepatic circulation.

Bile acids are absorbed passively from all of the gas-

trointestinal tract via ionic and non-ionic diffusion (255).

However, absorption of bile acids by non-ionic diff trointestinal 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 d riowever, absorption of bile acids by non-nonc 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 con-Hence the relative contribution of each process depends
on intraluminal and membrane pH, the dissociation con-
stant (pKa) of the individual bile acid, the maximal
solubilizing capacity of bile acid micelles for their own
 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 i stant (pKa) of the mutvidual 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
(1 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)
w ionic and non-ionic species into absorptive membra (160). In the upper small intestine with pH 5.5 to 6 about 50% of unconjugated bile acids (pKa 5.0 to 6 will be protonated and non-ionized; a small amount glycine-conjuga (160). In the upper small intestine with pH 5.5 to 6.8 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 protonate 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 proton ated; and no taurine derivatives (pKa $\lt 1.8$) will be n will be protonated and non-ionized; a singlycine-conjugated acids (pKa 3.5 to 5.2) ated; and no taurine derivatives (pKa $<$ 1.
ionized. To be absorbed by passive diffusionized bile acids must remain in solution.
The ated; 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 conju-

Example the Ref. This prescript the actor of the entero-
hepatic cycling of bile acids was strengthened by discov-
ery of the bile acids in 1809 by Berzelius and their
enterohepatic circulation in 1937 by Sobotka and in 1 ated, and no tautine derivatives (pKa < 1.6) 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 conju-
gates, de 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 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 pasgates, 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 pas-
sive transport rates; the most polar bile acids wit In the lower third of the heun 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 transpor rates across the ileum while passively absorbed bile acids passive diffusion have the inglest 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 glucuroni-
 races across the health while passively absorbed bile actus
have lower active transport maximums (701). Bile acids
with two or more ionic substituents such as glucuroni-
dated or sulfated derivatives (247) are poorly absor with two or more ionic substituents such as glucuro
dated or sulfated derivatives (247) are poorly absort
by either active or passive processes (407). Thus, the
are three enterohepatic circuits: one fast, one intern
diate, 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 absor are three enterohepatic circuits: one fast, one interme-
diate, 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 conju diate, and one slow (115) , as a high proportion of glycine conjugated dihydroxy bile acids are passively absorbed in the jejunum $(34, 35)$; taurine and glycine conjugated of di- and trihydroxy acids are actively absorb 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 will be protonated and non-ionized; a small amount of glycine-conjugated acids (pKa 3.5 to 5.2) will be proton-
ated; and no taurine derivatives (pKa < 1.8) will be non-
ionized. To be absorbed by passive diffusion, these

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). E 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). E sively taken up in the colon (600).

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 chenode portar vent and only heghgible 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 becau 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 av 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 lipoprote and the more efficient conservation of the less polar acids (21, 294, 497, 498). The bile acids bind avidly both serum albumin (294), high density lipoproteins, aperhaps low density lipoproteins (682). There is libinding t acids (21, 254, 457, 456). 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 lipop perhaps low density lives
binding to immunoglob
teins (682). Conjugated
to serum albumin at p
higher binding (294).
Hepatic uptake of mating to immunoglobulins or very low density lipopro-
ins (682). Conjugated and unconjugated bile acids bind
serum albumin at pH 7.4 with the free acid having
gher binding (294).
Hepatic uptake of bile acids is extremely

during (662). Conjugated and diffeomorphizated the actus 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 We seture about and that the 11-4 with the free actor having
higher binding (294).
during a single pass through the liver (497, 498, 779,
943). First-pass clearance in animals and humans is
greater than 90% for cholates an 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

aspet

BILE FORMATION, HEPATIC UPTAKE, AND BILIARY EXCRETION ⁴³

BILE FORMATION, HEPATIC UPT
uptake of bile acids is independent of their perfusate
level suggesting the liver's capacity to extract bile acids BILE FORMATION, HEPATIC UPTA
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 BILE FORMATION, HEPATIC UPTA
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 uptake of bile acids is independent of their perfusat
level suggesting the liver's capacity to extract bile acid
exceeds the transport maximum into bile (936). Hepati
uptake of bile acids usually functions with concentrati uptake of the actus is independent of their perfusable
level suggesting the liver's capacity to extract bile acide
exceeds the transport maximum into bile (936). Hepatic
uptake of bile acids usually functions with concent nodeoxycholates are cleared more slowly. Hepatic (9:36). Hepatic (9:48) uptake of bile acids usually functions with concentrations be well below V_{max} . Cholates are rapidly cleared and chenodeoxycholates are cleared more well below V_{max} . Cholates are rapidly cleared and che-
nodeoxycholates are cleared more slowly, suggesting that (1163), and sulindac (270, 271). The enterohepatic cir-
uptake is directly related to the polarity of the b wen below v_{max}. Cholates are rapidly cleared and che-
nodeoxycholates 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 nodeoxycholates are cleared more slowly, suggesting that
uptake is directly related to the polarity of the bile acid cu
and may also be inversely related to the strength of di
binding to albumin and lipoproteins (497, 498, uptake is urectly 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 b and may also
binding to albu
682, 779, 1013)
acid uptake ma
of this review. **B. Other Endogenous Compounds**
B. Other Endogenous Compounds
B. Other Endogenous Compounds
B. Other Endogenous Compounds
Several endogenous substances

In this review.

Several endogenous Compounds

Several endogenous substances other than bile acids

Several endogenous substances other than bile acids

e secreted into bile and undergo enterohepatic circuor this review.

B. Other Endogenous Compounds

Several endogenous substances other than bile aciare

are secreted into bile and undergo enterohepatic circu-

lation. Bile is the major excretory route for 1,25-dih B. Other Endogenous Compounds
Several endogenous substances other than bile a
are secreted into bile and undergo enterohepatic ci
lation. Bile is the major excretory route for 1,25-d
droxyvitamin D₃ and its metabolites (B. Other Enaogenous compounds
Several endogenous substances other than bile acids
are secreted into bile and undergo enterohepatic circu-
lation. Bile is the major excretory route for 1,25-dihy-
droxyvitamin D_3 and its Several enlogenous substances other than the actus
are secreted into bile and undergo enterohepatic circulation. Bile is the major excretory route for 1,25-dihy-
droxyvitamin D₃ and its metabolites (46, 87, 745, 881). h are secreted into the and undergo enteronepatic circulation. Bile is the major excretory route for 1,25-dihy-
droxyvitamin D_3 and its metabolites (46, 87, 745, 881).
Enterohepatic recycling of 25-hydroxyvitamin D_3 h Hation. Die is the major excretory route for 1,25-diny-
droxyvitamin 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, 7 and man. Paya and its metabolites (40, 61, 140, 661).
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
a Enteronepatic 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 ex-
c been demonstrated in man (45) and for $1,25$ - $(055, 745, 1260)$ and $24,25$ -dihydroxyvitamin D_3 (692) in the rat and man. Prostacyclin and several metabolites are excreted into bile after *p*-oxidation and glucuronid and man. Prostacyclin and several metabolites are ex-
creted into bile after p -oxidation and glucuronidation
and seem to undergo enterohepatic circulation (1167).
The coenzyme 5-methyltetrahydrofolate undergoes car-
rie and man. Frostacyclin and several metabolities are excreted into bile after *p*-oxidation and glucuronidation
and seem to undergo enterohepatic circulation (1167).
The coenzyme 5-methyltetrahydrofolate undergoes car-
rierand seem to undergo enterohepatic circulation (1167).

The coenzyme 5-methyltetrahydrofolate undergoes car-

rier-mediated hepatic uptake, secretion into bile against

a high concentration gradient, and enterohepatic cycl and seem to undergo enteronepatic circulation (1107).
The coenzyme 5-methyltetrahydrofolate undergoes care-
mediated hepatic uptake, secretion into bile agains
a high concentration gradient, and enterohepatic cyclin
(1131, The coenzyme 3-methytetranyarolotate undergoes
rier-mediated hepatic uptake, secretion into bile aga
a high concentration gradient, and enterohepatic cyc
(1131, 1151). Enterohepatic circulations have been d
onstrated for p The Finemated hepatic uptake, secretion into the agains
a high concentration gradient, and enterohepatic cyclin
(1131, 1151). Enterohepatic circulations have been dem
onstrated for pregnenolone and its 3-sulfate, deoxycort (1131, 1151). Enterohepatic circulations have been demonstrated for pregnenolone and its 3-sulfate, deoxycorticosterone and corticosterone (304), hydroxycortisone and its metabolites (1286), norethindrone (1257), an-(1131, 1131). Enteronepatic circulations have been defined
onstrated for pregnenolone and its 3-sulfate, deoxycor
ticosterone and corticosterone (304), hydroxycortison
and its metabolites (1286), norethindrone (1257), an
 pounds are metabolized and are excreted predominantly as either glucuronide or sulfate conjugates. dicosterone and corticosterone (304), hy
and its metabolites (1286), norethindrol
drosterone, (781) and estrone (814). All
pounds are metabolized and are excreted
as either glucuronide or sulfate conjugates drosterone, (781

pounds are meta

as either glucure
 C. Xenobiotics

Although fore

C. Xenobiotics
Although foreign compounds undergo enterohepatic
cycling, few are actively reabsorbed in the intestine. 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 C. Xenobiotics

Compounds undergo enterohepatic

cycling, few are actively reabsorbed in the intestine. de

Compounds secreted into bile in lipid-soluble forms are

reabsorbed by passive diffusion. Generally, these sub-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 sub-
stances cycling, lew are actively reabsorbed in the intestine. dompounds secreted into bile in lipid-soluble forms are S
reabsorbed by passive diffusion. Generally, these sub-
stances are biotransformed and conjugated before excre 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. How stances are biotransformed and conjugated before excrestances are biotransiormed 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 tion. 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 bac-
 flowever, many compounds excreted as polar conjugates cyprover, many compounds excreted as polar conjugates cyproduction of glucuronic acid or sulfate may be hydrolyzed by bacterial β -glucuronidases or sulfatases prese Frowever, many compounds excrosion of glucuronic acid or sulfate material β -glucuronidases or sulfat flora (532), and the aglycone m
portal circulation (1107, 1266).
Examples of xenobiotics that glucuronic acid or sulfate may be nyarolyzed by bac-
rial β -glucuronidases or sulfatases present in bacterial
ra (532), and the aglycone may be taken up into the
rtal circulation (1107, 1266).
Examples of xenobiotics t

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 ethinyles-
tradiol $(140, 751)$ flora (532), and the aglycone may be taken up into the excress portal circulation (1107, 1266).

Examples of xenobiotics that undergo enterohepatic used

recirculation include estradiol, mestranol and ethinyles-

biliar
 portal circulation (1107, 1266).

Examples of xenobiotics that undergo enteroheparecirculation include estradiol, mestranol and ethinyle

tradiol (140, 751), norethisterone (48), estrone-sulfa

(49), propachlor (55, 713), Examples of xenobiotics that undergo enterohep-
recirculation include estradiol, mestranol and ethiny
tradiol (140, 751), norethisterone (48), estrone-suli
(49), propachlor (55, 713), aniline mustard (183), di
fenac (1188) recirculation include estradiol, mestranol and ethinyl
tradiol (140, 751), norethisterone (48), estrone-sulf
(49), propachlor (55, 713), aniline mustard (183), dic
fenac (1188), fenclofenac (417), morphine (898), phen
phth rradiol (140, 751), horethisterone (48), estrone-sulfate at (49), propachlor (55, 713), aniline mustard (183), diclo-
fenac (1188), fenclofenac (417), morphine (898), phenol-
phthalein (206, 898), diphenylacetic acid (898)

ette, AND BILIARY EXCRETION
Pyrene (182), chlordecone (448), numerous insecticides
(776, 783), 3,4,4'-trichlorocarbanilide (482), oxazepam KE, AND BILIARY EXCRETION 43
pyrene (182), chlordecone (448), numerous insecticides
(776, 783), 3,4,4'-trichlorocarbanilide (482), oxazepam
(99), lormetazepam (391), spironolactone (9), diethylstil-KE, AND BILIARY EXCRETION
pyrene (182), chlordecone (448), numerous insectio
(776, 783), 3,4,4'-trichlorocarbanilide (482), oxaze
(99), lormetazepam (391), spironolactone (9), diethyl
bestrol (345, 457), diphenylhydantoin pyrene (182), chlordecone (448), numerous insecticie
(776, 783), 3,4,4'-trichlorocarbanilide (482), oxazep
(99), lormetazepam (391), spironolactone (9), diethyls
bestrol (345, 457), diphenylhydantoin (295, 296), met
nidazo pyrene (152), chiordecone (445), numerous insecutives
(776, 783), 3,4,4'-trichlorocarbanilide (482), oxazepam
(99), lormetazepam (391), spironolactone (9), diethylstil-
bestrol (345, 457), diphenylhydantoin (295, 296), me (116, 163), 3,4,4 -trichiorocarbannique (462), Oxazepani
(99), lormetazepam (391), spironolactone (9), diethylstil-
bestrol (345, 457), diphenylhydantoin (295, 296), metro-
nidazole (712), l- α -acetylmethadol (996, 997) (55), formetazepam (551), spironolactone (5), diethylistic
bestrol (345, 457), diphenylhydantoin (295, 296), metro
nidazole (712), l- α -acetylmethadol (996, 997), adriamycin
(1163), and sulindac (270, 271). The enterohe nidazole (712), l- α -acetylmethadol (996, 997), adriamycin (1163) , and sulindac $(270, 271)$. The enterohepatic cir-

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 culation of morphine, methadone, etorphine, digitoxin,
diethylstilbestrol, indomethacin, glutethimide, amphet-
amine, and others have been reviewed (926).
Some heavy metals have been shown to undergo an
enterohepatic circu duethylistibestrol, indomethachi, gluethimide, 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 a 2 hours have been reviewed (320).

2 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 th Some neavy 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
(63 enteronepatic criculation (044). 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 dival 2 hours, yet less than 10% is in the feces within 1 we
(633). Approximately 35%, 21%, and 17% of the divale
cations of manganese, mercury, and copper, respective
are reabsorbed after biliary excretion (191). In addition
th (633). Approximately 35%, 21%, and 17% of the divalentions of manganese, mercury, and copper, respectivel are reabsorbed after biliary excretion (191). In addition the organic mercurials, phenyl- and methyl-mercur have a 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 halfthe organic mercurials, phenyl- and methyl-mercury,

rections, phenyi- and methyi-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 It has been suggested the long pharmacological half
life of digitoxin in humans results from its enterohepati
recycling (592, 593, 869). Although interrruption of thi
circulation leads to a reduced half-life, factors other 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 vari cycling (392, 393, 809). Although interrruption of this
culation leads to a reduced half-life, factors other than
terohepatic circulation are important in the slow elim-
ation of digitoxin (1142).
Large species variations

circulation leads to a reduced nail-life, factors other than
enterohepatic circulation are important in the slow elim-
ination of digitoxin (1142).
Large species variations exist in the biliary excretion
of many xenobiotic enteronepatic circulation are important in the slow efficiation of digitoxin (1142).

Large species variations exist in the biliary excret

of many xenobiotics and animal studies do not alw

reflect the human situation. Th hepatic cycling in humans has been limited to only a few drugs because of difficulties associated with prolonged Large species variations exist in the omary excretion
of many xenobiotics and animal studies do not always
reflect the human situation. The investigation of entero-
hepatic cycling in humans has been limited to only a few
 reflect the human situation. The investigation of entero-
hepatic cycling in humans has been limited to only a few
drugs because of difficulties associated with prolonged
interruption of the enterohepatic circulation. drugs because of difficulties associated with prolonged
interruption of the enterohepatic circulation.
D. Factors Influencing Enterohepatic Cycling

fenac (1188), fenclofenac (417), morphine (898), phenol-
pine (847). Administration of a polythiol-binding resin
phthalein (206, 898), diphenylacetic acid (898), 2-aceta-
mido-4-(chloromethyl)thiazole (56), pentachloromet **1.** *Binding Agents.* Administration of activated char-D. Factors Influencing Enterohepatic Cycling
1. Binding Agents. Administration of activated char-
coal or anion-exchange resins can decrease enterohepatic
cycling of xenobiotics and can be clinically useful. Cho-D. Factors Influencing Enterohepatic Cycling
1. Binding Agents. Administration of activated char
coal or anion-exchange resins can decrease enterohepati
cycling of xenobiotics and can be clinically useful. Cho
lestyramine 1. Binding Agents. Administration of activated char-
coal or anion-exchange resins can decrease enterohepatic
cycling of xenobiotics and can be clinically useful. Cho-
lestyramine treatment of patients receiving ³H-digit 1. Binding Agents. Administration of activated char-
coal or anion-exchange resins can decrease enterohepatic
cycling of xenobiotics and can be clinically useful. Cho-
lestyramine treatment of patients receiving ³H-digit coal or allion-exchange results can decrease enteromepatic
cycling of xenobiotics and can be clinically useful. Cho-
lestyramine treatment of patients receiving ³H-digitoxin
decreases the serum half-life from 11.5 to 6.6 eyeting of xenobiotics and can be chincally useful. Cho-
lestyramine treatment of patients receiving ³H-digitoxin
decreases the serum half-life from 11.5 to 6.6 days (155).
Similar results have been obtained with chlorde 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).
 decreases the serum han-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
 Similar results have been obtained with chloroecon
(129, 204), phenoprocoumon (799), and bile acids (561
In fact, bile acid depletion by cholestyramine has bee
shown to decrease the biliary excretion of numerot
organic ani (129, 204), phenoprocoumon (199), and one acids (3)
In fact, bile acid depletion by cholestyramine has $\frac{1}{2}$
shown to decrease the biliary excretion of nume
organic anions including BSP, bromcresol green, in
cyanine g In fact, one acid depletion by cholestyramine has been
shown to decrease the biliary excretion of numerous
organic anions including BSP, bromcresol green, indo-
cyanine green, rose bengal, and eosine (421). Cholesty-
ramin shown to decrease the binary excretion of numerous
organic anions including BSP, bromcresol green, indo-
cyanine green, rose bengal, and eosine (421). Cholesty-
ramine-induced interruption of enterohepatic cycling
produces organic anions including BSP, bromcresol green, inc
cyanine green, rose bengal, and eosine (421). Cholest
ramine-induced interruption of enterohepatic cycli
produces a two- and seven-fold increase in the fee
excretions of cyanine green, rose bengal, and eosine (421). Cholesty-
ramine-induced interruption of enterohepatic cycling
produces a two- and seven-fold increase in the fecal
excretions of phenprocoumon and chlordecone, respec-
tively ramine-induced interruption of enteronepatic cycling
produces a two- and seven-fold increase in the fecal
excretions of phenprocoumon and chlordecone, respec-
tively (129, 204, 799). Activated charcoal has also been
used t produces a two- and seven-rold increase in the recalence excretions of phenprocoumon and chlordecone, respectively (129, 204, 799). Activated charcoal has also been used to trap drugs in the gastrointestinal tract after th lively (125, 204, 755). 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 binary excretion. Atthough peak blood levels are not
affected significantly, charcoal reduces the serum half-
life of phenylbutazone, phenobarbital, and carbamaze-
pine (847). Administration of a polythiol-binding resin
to life of phenylbutazone, phenobarbital, and carbamazeto mice greatly increases the fecal excretion and reduces

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KLAASSEN A

of these binding agents is a practical means for detoxi-

cation of animals and patients exposed to toxicants.

More recent studies indicate administration of ali-

phatic hydrocarbons such as mineral oil and h of these binding agents is a practical means for detox
cation of animals and patients exposed to toxicants.
More recent studies indicate administration of al
phatic hydrocarbons such as mineral oil and hexadecane
which are of these binding agents is a practical means for detoxication of animals and patients exposed to toxicants. In More recent studies indicate administration of ali-

phatic hydrocarbons such as mineral oil and hexadecane, wi cation of animals and patients exposed to toxicants.
More recent studies indicate administration of ali-
phatic hydrocarbons such as mineral oil and hexadecane,
which are poorly absorbed by the gut, can enhance the
fecal e more recent studies indicate administration of an-
phatic hydrocarbons such as mineral oil and hexadecane,
which are poorly absorbed by the gut, can enhance the
fecal excretion of lipophilic xenobiotics. For example,
prese phatic nydrocarbons such as mineral off and nexadecane, will
which are poorly absorbed by the gut, can enhance the isol
fecal excretion of lipophilic xenobiotics. For example, her
presence of 5% mineral oil in the diet of 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), a 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
hexachlorophenzene (1006). Similar results have been (1010), $2,4,5,2',4',5'$ -hexabromobiphenyl (1008), and acterize these carriers and ascertain how these are func-
hexachlorobenzene (1006). Similar results have been ob-
served after 4% cholestyramine for pentachlorophenol a (1010), $2,4,5,2',4',5'$ -hexabromobiphenyl (1008), and
hexachlorobenzene (1006). Similar results have been ob-
served after 4% cholestyramine for pentachloropheno
(1009) and hexadecane for hexachlorobenzene in rats
and rhes hexachlorobenzene (1006). Similar results have been
served after 4% cholestyramine for pentachloroph
(1009) and hexadecane for hexachlorobenzene in
and rhesus monkeys (1005, 1006). Mineral oil and
adecane also decreased th served after 4% cholestyramine for pentachlorophenol and (1009) and hexadecane for hexachlorobenzene in rats of and rhesus monkeys (1005 , 1006). Mineral oil and hexadecane also decreased the body burden of hexach (1003) and nexaded
and rhesus monkeys
adecane also decreas
benzene in sheep (1
agents in the feces.
Similar cycling pr Interests monkeys (1000, 1000). Minteral on and hex-
ecane also decreased the body burden of hexachloro-
nzene in sheep (1007) presumably by trapping these
ents in the feces.
Similar cycling probably exists for many therap

benzene 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 pharmacody-
namics of each drug will have to await ex agents but the relative importance to the pharmacody-
namics 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, investigation in the recess.

Similar cycling probably exists for many therapeutic W

agents but the relative importance to the pharmacody-

namics of each drug will have to await experimental

investigation in humans. Use agents out the relative importance to the pharmacody-
namics 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 f mannes 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 excretor Proposition of xenobiotic toxicity is efficacious, and may,
 fact, further our understanding of the biliary excretory

ocesses and enterohepatic circulation of drugs and
 2. Antibiotics. Although hepatic biotransformat

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 ent toxicants in humans.

2. Antibiotics. Although hepatic biotransformation to

more polar forms decreases the enterohepatic circulation,

intestinal bacteria are sometimes able to convert xeno-

biotics back into their lipid biotics back in humans.

2. Antibiotics. Although hepatic biotransformation to

more polar forms decreases the enterohepatic circulation,

intestinal bacteria are sometimes able to convert xeno-

biotics back into their li 2. Antibiotics. Although hepatic biotransiormation to
more polar forms decreases the enterohepatic circulation,
intestinal bacteria are sometimes able to convert xeno-
biotics back into their lipid-soluble forms and enhanc more polar forms decreases the enterohepatic circulaties
intestinal bacteria are sometimes able to convert xe
biotics back into their lipid-soluble forms and enha
reabsorption (1106, 1266). Alterations in intestinal fl
wit mesulian bacteria are sometimes able to convert keno-
biotics back into their lipid-soluble forms and enhance
reabsorption (1106, 1266). Alterations in intestinal flora
with antibiotics may decrease the enterohepatic circu reabsorption (1106, 1266). Alterations in intestinal flora
with antibiotics may decrease the enterohepatic circula-
tion of some xenobiotics and concurrently shorten their
pharmacological half-lives. Use of antibiotics in tion or some xenonotics 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 pharmacological nair-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 enteronepatic 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
o 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 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
re the parent compound correlate with decreased numb
of microflora and last 3 to 4 days with rifampicin or 7
14 days with ampicillin (48). These two antibiotics a
excreted into bile and may undergo an enterohepa
recirculation 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 de 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 appropriat one and may undergo an external (1107). Numerous studies h
nicroorganisms are capable of
otransformations in vivo and in
IX. Concluding Remarks
data have been published rec rated that microorganisms are capable of performing
propriate biotransformations in vivo and in vitro (532).
IX. Concluding Remarks
Much new data have been published recently which
eatly expand our understanding of biliary

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 he IX. Concluding Hemarks
Much new data have been published recently which
greatly expand our understanding of biliary excretion
However, this knowledge about hepatic elimination lag
behind that regarding mechanisms of secret Much new data have been published recently w
greatly expand our understanding of biliary excre
However, this knowledge about hepatic elimination
behind that regarding mechanisms of secretion of α
pounds by the kidney an greatly expand our understanding of biliary excretion.

However, this knowledge about hepatic elimination lags

behind that regarding mechanisms of secretion of com-

pounds by the kidney and hepatic and renal biotransfor-However, this knowledge about hepatic elimination lags
behind that regarding mechanisms of secretion of com-
pounds by the kidney and hepatic and renal biotransfor-
mation. Major obstacles hindering our search for new
info 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 pounds 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 inab mation. 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,
p 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 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 for-
 inability to sample bile at various places in the liver, particularly the canaliculus. Unfortunately, we still do not completely comprehend the mechanisms of bile for-
mation which would aid our understanding of biliary ex

D WATKINS
siderable information has been gathered about factors
influencing biliary excretion and mechanisms of hepatic D WATKINS
siderable information has been gathered about factors
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will be to utilize sophisticated biochemical techniques to
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