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# Vol. 47, No. 1<br>Copyright © 1995 by The American Society for Pharmacology and Experimental Therapeutics<br>**Diabetes Mellitus-Induced Alterations of Hepatobiliary Function** Function<br>Function<br>JOHN B. WATKINS III\* AND R. A. SANDERS<br>Indiana University School of Medicine *I***' UNCTION**<br>*In B. WATKINS III\* AND R. A. SANDER*<br>*Indiana University School of Medicine*



**I. Introduction**<br>Diabetes mellitus may be defined as a commonly oc-I. Introduction<br>Diabetes mellitus may be defined as a commonly oc-<br>rring disease in which plasma glucose control is de-I. Introduction<br>Diabetes mellitus may be defined as a commonly oc-<br>curring disease in which plasma glucose control is de-<br>fective because of insulin deficiency or decreased target**fective because of insuling the insuline defined** as a commonly curring disease in which plasma glucose control is fective because of insulin deficiency or decreased targetal responsiveness to insulin. Diabetes is of Creament Calculation<br>Curring disease in which plasma glucose control is de-<br>fective because of insulin deficiency or decreased target-<br>cell responsiveness to insulin. Diabetes is often manacompanied by diverse pathological Diabetes mellitus may be defined as a commonly oc-<br>curring disease in which plasma glucose control is de-<br>fective because of insulin deficiency or decreased target-<br>cell responsiveness to insulin. Diabetes is often<br>accomp curring disease in which plasma glucose control is<br>fective because of insulin deficiency or decreased tar<br>cell responsiveness to insulin. Diabetes is c<br>accompanied by diverse pathological states, inclu<br>coronary heart disea fective because of insulin deficiency or decreased target-<br>cell responsiveness to insulin. Diabetes is often<br>accompanied by diverse pathological states, including<br>coronary heart disease, renal insufficiency, cerebrovas-<br>cu cell responsiveness to insulin. Diabetes is of accompanied by diverse pathological states, includ coronary heart disease, renal insufficiency, cerebrov cular disorders, and neuropathy. Diabetes is also knot to produce subs accompanied by diverse pathological states, including<br>coronary heart disease, renal insufficiency, cerebrovas-<br>cular disorders, and neuropathy. Diabetes is also known<br>to produce substantial changes in intracellular metabo-**1980**<br> **1990**). Because of the importance of bilary excretionally fractionally interesting to produce substantial changes in intracellular metabolitary<br> **1990**). Because of the importance of biliary excretion in<br>
the remo cular disorders, and neuropathy. Diabetes is also known<br>to produce substantial changes in intracellular metabo-<br>lism in most tissues, including liver (Rifkin and Porte,<br>1990). Because of the importance of biliary excretio to produce substantial changes in intracellular metabolism in most tissues, including liver (Rifkin and Porte,  $\frac{D\xi}{1990}$ ). Because of the importance of biliary excretion in the removal of drugs and their metabolites lism in most tissues, including liver (Rifkin and Porte, 1990). Because of the importance of biliary excretion in the removal of drugs and their metabolites from the body (Siegers and Watkins, 1991), several studies on th 1990). Because of the importance of biliary excretion ithe removal of drugs and their metabolites from the body (Siegers and Watkins, 1991), several studies on the effects of insulin deficiency on hepatic drug disposition body (Siegers and Watkins, 1991), several studies on the effects of insulin deficiency on hepatic drug disposition provide evidence that diabetes may also alter the pharmaceutical macodynamics and pharmacekinetics of phar macodynamics and pharmacokinetics of pharmaceutical<br>agents (Watkins and Sanders, 1991), potentially in-<br>\* To whom correspondence should be addressed: Medical Sciences

creasing the risk of drug<br>decreasing drug efficacy.<br>Early researchers four

Easing the risk of drug toxicity and side effects or<br>ereasing drug efficacy.<br>Early researchers found an increased incidence of<br>llstones in diabetics at autopsy (Feldman and Feldcreasing the risk of drug toxicity and side effects decreasing drug efficacy.<br>
Early researchers found an increased incidence at autopsy (Feldman and Feldman, 1954; Lieber, 1952), as well as an increased frequency creasing the risk of drug toxicity and side effects or<br>decreasing drug efficacy.<br>Early researchers found an increased incidence of<br>gallstones in diabetics at autopsy (Feldman and Feld-<br>man, 1954; Lieber, 1952), as well as decreasing drug efficacy.<br>Early researchers found an increased incidence<br>gallstones in diabetics at autopsy (Feldman and Fel<br>man, 1954; Lieber, 1952), as well as an increased fi<br>quency of cholelithiasis among diabetic pati Early researchers found an increased incidence of gallstones in diabetics at autopsy (Feldman and Feldman, 1954; Lieber, 1952), as well as an increased frequency of cholelithiasis among diabetic patients (Goldstein and Sch gallstones in diabetics at autopsy (Feldman and Feldman, 1954; Lieber, 1952), as well as an increased frequency of cholelithiasis among diabetic patients (Goldstein and Schein, 1963; Twiss and Carter, 1952). Diabetes-induc man, 1954; Lieber, 1952), as well as an increased frequency of cholelithiasis among diabetic patients (Goldstein and Schein, 1963; Twiss and Carter, 1952).<br>Diabetes-induced changes have been observed in biotransformation, quency of cholelithiasis among diabetic patients (Goldstein and Schein, 1963; Twiss and Carter, 1952).<br>Diabetes-induced changes have been observed in bio-<br>transformation, both in humans (Daintith et al., 1976;<br>Dajani et al stein and Schein, 1963; Twiss and Carter, 1952).<br>Diabetes-induced changes have been observed in bio-<br>transformation, both in humans (Daintith et al., 1976;<br>Dajani et al., 1974; Oltmanns et al., 1984; Salmela et al.,<br>1980) Diabetes-induced changes have been observed in bio-<br>transformation, both in humans (Daintith et al., 1976;<br>Dajani et al., 1974; Oltmanns et al., 1984; Salmela et al.,<br>1980) and in laboratory animal models (Ackerman and<br>Lei transformation, both in humans (Daintith et al., 1976;<br>Dajani et al., 1974; Oltmanns et al., 1984; Salmela et al.,<br>1980) and in laboratory animal models (Ackerman and<br>Leibman, 1977; Emudianughe et al., 1988; Faas and<br>Carte Dajani et al., 1974; Oltmanns et al., 1984; Salmela et al., 1980) and in laboratory animal models (Ackerman and Leibman, 1977; Emudianughe et al., 1988; Faas and Carter, 1980; Grant and Duthie, 1987; Past and Cook, 1982; R 1980) and in laboratory animal models (Ackerman and Leibman, 1977; Emudianughe et al., 1988; Faas and Carter, 1980; Grant and Duthie, 1987; Past and Cook, 1982; Rouer et al., 1982; Watkins et al., 1988). Also, alterations Leibman, 1977; Emudianughe et al., 1988; Faas and Carter, 1980; Grant and Duthie, 1987; Past and Cook, 1982; Rouer et al., 1982; Watkins et al., 1988). Also, alterations in pharmacokinetic parameters have been noted for va Carter, 1980; Grant and Duthie, 1987; Past and Cook, 1982; Rouer et al., 1982; Watkins et al., 1988). Also, alterations in pharmacokinetic parameters have been noted for various drugs and xenobiotics (Carnovale et al., 198 1982; Rouer et al., 1982; Watkins et al., 1988). Also, alterations in pharmacokinetic parameters have been noted for various drugs and xenobiotics (Carnovale et al., 1986; Dajani et al., 1974; Uchida et al., 1979; Watkins alterations in pharmacokinetic parameters have<br>noted for various drugs and xenobiotics (Carnov<br>al., 1986; Dajani et al., 1974; Uchida et al.,<br>Watkins and Dykstra, 1987; Watkins and Noda,<br>Watkins and Sherman, 1992; Wey et a ted for various drugs and xenobiotics (Carnovale et<br>
., 1986; Dajani et al., 1974; Uchida et al., 1979;<br>
atkins and Dykstra, 1987; Watkins and Noda, 1986;<br>
atkins and Sherman, 1992; Wey et al., 1984).<br>
This paper will pres

Watkins and Dykstra, 1987; Watkins and Noda, 1986;<br>
\*To whom correspondence should be addressed: Medical Sciences<br>
Program, Indiana University School of Medicine, Bloomington, IN<br>
+ To whom correspondence should be address al., 1986; Dajani et al., 1974; Uchida et al., 1979;<br>Watkins and Dykstra, 1987; Watkins and Noda, 1986;<br>Watkins and Sherman, 1992; Wey et al., 1984).<br>This paper will present a simplified overview of bile<br>formation, hepatic Watkins and Dykstra, 1987; Watkins and Noda, 1986;<br>Watkins and Sherman, 1992; Wey et al., 1984).<br>This paper will present a simplified overview of bile<br>formation, hepatic uptake, and biliary excretion in order<br>to facilitate Watkins and Sherman, 1992; Wey et al., 1984).<br>This paper will present a simplified overview of bile<br>formation, hepatic uptake, and biliary excretion in order<br>to facilitate understanding diabetes-related effects on<br>these fu This paper will present a simplified overview of bile<br>formation, hepatic uptake, and biliary excretion in order<br>to facilitate understanding diabetes-related effects on<br>these functions. Extensive discussions of the general<br>

<sup>47405</sup> <sup>\*</sup> To whom correspondence should be addressed: Medical Scienc<br>ogram, Indiana University School of Medicine, Bloomington,<br>405<br>† Abbreviations: ATP, adenosine triphosphate; ATPase, aden<br>e triphosphatase; v<sub>max</sub>, maximal vel \* To whom correspondence should be addressed: Medical Science Program, Indiana University School of Medicine, Bloomington, I<br>47405<br>† Abbreviations: ATP, adenosine triphosphate; ATPase, aden<br>sine triphosphatase;  $v_{max}$ , ma

**phate.**

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et al., 1988; Boyer et al., 1992; Coleman and Rahman,<br>1992; Klaassen and Watkins, 1984; Meijer and Van der <sup>2</sup> WATKINS AND S4<br>
1992; Klaassen and Watkins, 1984; Meijer and Van der<br>
1992; Klaassen and Watkins, 1984; Meijer and Van der<br>
1989; Petzinger et al., 1989a; Siegers and Tre<br>
Watkins, 1991). A more exhaustive review of th et al., 1988; Boyer et al., 1992; Coleman and Rahma<br>1992; Klaassen and Watkins, 1984; Meijer and Van de<br>Sluijs, 1989; Petzinger et al., 1989a; Siegers an<br>Watkins, 1991). A more exhaustive review of the avail<br>able data rega et al., 1988; Boyer et al., 1992; Coleman and Rahman, most 1992; Klaassen and Watkins, 1984; Meijer and Van der chon Sluijs, 1989; Petzinger et al., 1989a; Siegers and Treations, 1991). A more exhaustive review of the avai 1992; Klaassen and Watkins, 1984; Meijer and Van der clups, 1989; Petzinger et al., 1989a; Siegers and T<br>Watkins, 1991). A more exhaustive review of the available data regarding diabetes-induced alterations in whepatobilia Watkins, 1991). A more exhaustive review of the available data regarding diabetes-induced alterations in hepatobiliary function as well as suggestions for future research will also be presented here.

# **II. Streptozotocin-** and **Afloxan-induced Diabetes**

Insulin-dependent diabetes mellitus is characterized **II. Streptozotocin- and Alloxan-induced Diabetes**<br>Insulin-dependent diabetes mellitus is characterized<br>by low or absent levels of circulating endogenous insulin,<br>and injection of insulin helps control hyperglycemia and **II. Streptozotocin- and Alloxan-induced Diabetes** ficing the ficing insulin-dependent diabetes mellitus is characterized anisoly low or absent levels of circulating endogenous insulin, strand injection of insulin helps co I. Streptozotocin- and Alloxan-Induced Diabeter<br>Insulin-dependent diabetes mellitus is characterize<br>by low or absent levels of circulating endogenous insulir<br>and injection of insulin helps control hyperglycemia an<br>ketosis Insulin-dependent diabetes mellitus is characterized<br>by low or absent levels of circulating endogenous insulin<br>and injection of insulin helps control hyperglycemia and<br>ketosis as well as sustain life itself. Although the e by low or absent levels of circulating endogenous insulin, strand injection of insulin helps control hyperglycemia and now<br>ketosis as well as sustain life itself. Although the etiol-<br>ogy is unknown, human leukocyte antigen and injection of insulin helps control hyperglycemia and<br>ketosis as well as sustain life itself. Although the etiol-<br>ogy is unknown, human leukocyte antigen association<br>viral factors, and various environmental factors may<br> ketosis as well as sustain life itself. Although the etiogy is unknown, human leukocyte antigen association wiral factors, and various environmental factors montribute. There is chronic autoimmunity against pareatic islet ogy is unknown, human leukocyte antigen association,<br>viral factors, and various environmental factors may<br>contribute. There is chronic autoimmunity against pan-<br>creatic islet cells, and islet cell antibodies may be detectviral factors, and various environmental factors may et a contribute. There is chronic autoimmunity against pan-<br>creatic islet cells, and islet cell antibodies may be detect-<br>able years before clinical onset of the diseas contribute. There is chronic autoimmunity against pancreatic islet cells, and islet cell antibodies may be detectable years before clinical onset of the disease. Normally, insulin functions in opposition to glucagon, as th creatic islet cells, and islet cell antibodies may be detect-<br>able years before clinical onset of the disease. Normally,<br>insulin functions in opposition to glucagon, as the two<br>hormones function in concert to maintain norm able years before clinical onset of the disease. Normally, often insulin functions in opposition to glucagon, as the two sugn hormones function in concert to maintain normal glu-<br>cose metabolism. In the absence of insulin, insulin functions in opposition to glucagon, as the two hormones function in concert to maintain normal glucose metabolism. In the absence of insulin, there is express glucagon and a hormonal milieu that favors a increase hormones function in concert to maintain normal glu-<br>cose metabolism. In the absence of insulin, there is ex-<br>cess glucagon and a hormonal milieu that favors an<br>increase in hepatic gluconeogenesis and glycogenolysis,<br>a dec cose metabolism. In the absence of insulin, there is<br>cess glucagon and a hormonal milieu that favors<br>increase in hepatic gluconeogenesis and glycogenoly<br>a decrease in peripheral glucose uptake, and a decrea<br>conversion of g cess glucagon and a hormonal milieu that favors a<br>increase in hepatic gluconeogenesis and glycogenolysi<br>a decrease in peripheral glucose uptake, and a decrease<br>conversion of glucose into glycogen. Another pathogm<br>monic fea increase in hepatic gluconeogenesis and glycogenolysis,<br>a decrease in peripheral glucose uptake, and a decreased<br>conversion of glucose into glycogen. Another pathogno-<br>monic feature is thickening of capillary basement mema decrease in peripheral glucose uptake, and a decreased<br>conversion of glucose into glycogen. Another pathognomomic feature is thickening of capillary basement mem-<br>from branes. Moreover, conversion of excess glucose into monic feature is thickening of capillary basement membranes. Moreover, conversion of excess glucose into sorbitol may be involved in diabetic neuropathy and retinopathy (Rifkin and Porte, 1990).<br>Two experimental models hav onic feature is thickening of capillary basement mem-<br>anes. Moreover, conversion of excess glucose into sor-<br>tol may be involved in diabetic neuropathy and<br>tinopathy (Rifkin and Porte, 1990).<br>Two experimental models have b

branes. Moreover, conversion of excess glucose into s<br>bitol may be involved in diabetic neuropathy a<br>retinopathy (Rifkin and Porte, 1990).<br>Two experimental models have been extensively us<br>to determine how insulin deficienc retinopathy (Rifkin and Porte, 1990).<br>Two experimental models have been extensively used<br>to determine how insulin deficiency may affect hepato-<br>biliary function. Although early workers thought that<br>administration of alloxa retinopathy (Rifkin and Porte, 1990).<br>Two experimental models have been extensively used<br>to determine how insulin deficiency may affect hepato-<br>biliary function. Although early workers thought that<br>administration of alloxa Two experimental models have been extensively used<br>to determine how insulin deficiency may affect hepato-<br>biliary function. Although early workers thought that<br>administration of alloxan or streptozotocin induced sim-<br>ilar to determine how insulin deficiency may affect hepato-<br>biliary function. Although early workers thought that<br>administration of alloxan or streptozotocin induced sim-<br>ilar types of insulin-deficiency diabetes, there are maj biliary function. Although early workers thought that administration of alloxan or streptozotocin induced similar types of insulin-deficiency diabetes, there are major differences in their diabetogenic effects (Rerup, 1980 administration of alloxan or streptozotocin induced similar types of insulin-deficiency diabetes, there are major differences in their diabetogenic effects (Rerup, 1980; Shafrir, 1990). It has been known for some time that ilar types of insulin-deficiency diabetes, there are major low<br>differences in their diabetogenic effects (Rerup, 1980; He<br>Shafrir, 1990). It has been known for some time that cho<br>structural alterations in the beta cells of differences in their diabetogenic effects (Rerup, 1980;<br>Shafrir, 1990). It has been known for some time that<br>structural alterations in the beta cells of the pancreas<br>occur within 48 h of administration of streptozotocin a structural alterations in the beta cells of the pancreas bile acids and through cholesterol secretion into the bile;<br>occur within 48 h of administration of streptozotocin and cholesterol is either reabsorbed from the intes structural alterations in the beta cells of the pancreas<br>occur within 48 h of administration of streptozotocin and<br>last for up to 4 months, progressing finally to total<br>degranulation of beta cells (Arison et al., 1967). Al occur within 48 h of administration of streptozotocin and clast for up to 4 months, progressing finally to total degranulation of beta cells (Arison et al., 1967). Alloxan causes a decrease in hepatic glycogen within 24 to last for up to 4 months, progressing finally to total degranulation of beta cells (Arison et al., 1967). Alloxan causes a decrease in hepatic glycogen within 24 to 72 h, an effect that is partially reversible by insulin (D degranulation of beta cells (Arison et al., 1967). Alloxan causes a decrease in hepatic glycogen within 24 to 72 h<br>an effect that is partially reversible by insulin (Dixon e<br>al., 1961). Streptozotocin is more specific than causes a decrease in hepatic glycogen within 24 to 72 h, the an effect that is partially reversible by insulin (Dixon et 1<br>al., 1961). Streptozotocin is more specific than alloxan,<br>less likely to cause ketosis, and less pr an effect that is partially reversible by insulin (Dixon et 1983)<br>al., 1961). Streptozotocin is more specific than alloxan, D<br>less likely to cause ketosis, and less prone to interanimal 1999<br>variability in terms of effecti al., 1961). Streptozotocin is more specific than alloxan,<br>less likely to cause ketosis, and less prone to interanimal<br>variability in terms of effective dose. Alloxan generally<br>produces greater cytotoxicity owing to its con less likely to cause ketosis, and less prone to interanimal<br>variability in terms of effective dose. Alloxan generally<br>produces greater cytotoxicity owing to its conversion to<br>anionic radicals (Nukatsuka et al., 1989). Panc variability in terms of effective dose. Alloxan general produces greater cytotoxicity owing to its conversion<br>anionic radicals (Nukatsuka et al., 1989). Pancrealiste cells treated with alloxan exhibit multiple cellu<br>necros produces greater cytotoxicity owing to its conversion to 19<br>anionic radicals (Nukatsuka et al., 1989). Pancreatic de<br>islet cells treated with alloxan exhibit multiple cellular al<br>necrosis, marked degranulation, and extensi anionic radicals (Nukatsuka et al., 1989). Pancreatic dislet cells treated with alloxan exhibit multiple cellular and extensive vesiculation of the endoplasmic reticulum and Golgi complex, as likell as enlarged mitochondri islet cells treated with alloxan exhibit multiple cellular<br>necrosis, marked degranulation, and extensive vesicula-<br>tion of the endoplasmic reticulum and Golgi complex, as<br>well as enlarged mitochondria with disrupted crista necrosis, marked degranulation, and extensive vesiculation of the endoplasmic reticulum and Golgi complex, as<br>well as enlarged mitochondria with disrupted cristae<br>and mitochondrial ruptures (Abdel-Rahman et al.,<br>1992). Win tion of the endoplasmic reticulum and Golgi complex, as lipowell as enlarged mitochondria with disrupted cristae zate and mitochondrial ruptures (Abdel-Rahman et al., and 1992). Winkler and Moser (1992) suggest that disrup well as enlarged mitochondria with disrupted crist<br>and mitochondrial ruptures (Abdel-Rahman et a<br>1992). Winkler and Moser (1992) suggest that disruption<br>of the antioxidant tissue defense enzymes is central<br>the diabetogenic and mitochondrial ruptures (Abdel-Rahman et al., and A-1992). Winkler and Moser (1992) suggest that disruption erbated of the antioxidant tissue defense enzymes is central to ever, a the diabetogenic effect of streptozotoc

) SANDERS<br>most of the cytotoxic effects of alloxan, although mito-<br>chondria are still enlarged (Abdel-Rahman et al., 1992 Chondria are still enlarged (Abdel-Rahman et al., 1992).<br>Chondria are still enlarged (Abdel-Rahman et al., 1992).<br>Treatment of diabetic rats with vitamin E or probucol SANDERS<br>
most of the cytotoxic effects of alloxan, although mito-<br>
chondria are still enlarged (Abdel-Rahman et al., 1992).<br>
Treatment of diabetic rats with vitamin E or probucol<br>
alleviates the oxidation of lipoproteins a most of the cytotoxic effects of alloxan, although mito-<br>chondria are still enlarged (Abdel-Rahman et al., 1992).<br>Treatment of diabetic rats with vitamin E or probucol<br>alleviates the oxidation of lipoproteins and cytotoxic most of the cytotoxic effects of alloxan, although mito-<br>chondria are still enlarged (Abdel-Rahman et al., 1992).<br>Treatment of diabetic rats with vitamin E or probucol<br>alleviates the oxidation of lipoproteins and cytotoxic 1989). Freatment of diabetic rats with vitamin E or probucol<br>leviates the oxidation of lipoproteins and cytotoxicity<br>thout altering hyperglycemia (Morel and Chisolm,<br>89).<br>Interpretation of studies in chemically induced dia-<br>tic a

alleviates the oxidation of lipoproteins and cytotoxic<br>without altering hyperglycemia (Morel and Chisol<br>1989).<br>Interpretation of studies in chemically induced d<br>betic animals must consider the toxicity of the diabe<br>genic a without altering hyperglycemia (Morel and Chisolm, 1989).<br>
Interpretation of studies in chemically induced dia-<br>
betic animals must consider the toxicity of the diabeto-<br>
genic agents when determining the effect of insulin 1989).<br>Interpretation of studies in chemically induced diabetic animals must consider the toxicity of the diabeto-<br>genic agents when determining the effect of insulin de-<br>ficiency. Many studies of diabetic effects have use Interpretation of studies in chemically induced diabetic animals must consider the toxicity of the diabeto-<br>genic agents when determining the effect of insulin de-<br>ficiency. Many studies of diabetic effects have used<br>anima betic animals must consider the toxicity of the diabett genic agents when determining the effect of insulin deficiency. Many studies of diabetic effects have use animals from 1 day to 3 months after treatment wit streptozo genic agents when determining the effect of insulin deficiency. Many studies of diabetic effects have used<br>animals from 1 day to 3 months after treatment with<br>streptozotocin or alloxan. Effects on both bile flow (Car-<br>nova animals from 1 day to 3 months after treatment with<br>streptozotocin or alloxan. Effects on both bile flow (Car-<br>novale and Rodriguez-Garay, 1984; Carnovale et al.,<br>1987, 1991; Chawalit et al., 1982) and biliary excretion<br>(C animals from 1 day to 3 months after treatment with<br>streptozotocin or alloxan. Effects on both bile flow (Car-<br>novale and Rodriguez-Garay, 1984; Carnovale et al.,<br>1987, 1991; Chawalit et al., 1982) and biliary excretion<br>(C streptozotocin or alloxan. Effects on both bile flow (Carnovale and Rodriguez-Garay, 1984; Carnovale et al., 1987, 1991; Chawalit et al., 1982) and biliary excretion (Carnovale et al., 1986, 1987; Marin et al., 1988; Siege novale and Rodriguez-Garay, 1984; Carnovale et al., 1987, 1991; Chawalit et al., 1982) and biliary excretion (Carnovale et al., 1986, 1987; Marin et al., 1988; Siegers et al., 1985), as well as on hepatic biotransformation 1987, 1991; Chawalit et al., 1982) and biliary excretion<br>(Carnovale et al., 1986, 1987; Marin et al., 1988; Siegers<br>et al., 1985), as well as on hepatic biotransformation<br>(Badawy and Evans, 1977; Carnovale et al., 1992;<br>Uc (Carnovale et al., 1986, 1987; Marin et al., 1988; Sieger<br>et al., 1985), as well as on hepatic biotransformatio<br>(Badawy and Evans, 1977; Carnovale et al., 1992<br>Uchida et al., 1979) at 1 to 2 weeks after treatment ar<br>often (Badawy and Evans, 1977; Carnovale et al., 1992; Uchida et al., 1979) at 1 to 2 weeks after treatment are often not completely reversible by insulin treatment, suggesting that the damage may be owing to toxicity of the di (Badawy and Evans, 1977; Carnovale et al., 1992; Uchida et al., 1979) at 1 to 2 weeks after treatment are often not completely reversible by insulin treatment, suggesting that the damage may be owing to toxicity of the dia Uchida et al., 1979) at 1 to 2 weeks after treatment are<br>often not completely reversible by insulin treatment,<br>suggesting that the damage may be owing to toxicity of<br>the diabetogen rather than diabetes itself. However,<br>man often not completely reversible by insulin treatment<br>suggesting that the damage may be owing to toxicity of<br>the diabetogen rather than diabetes itself. However<br>many signs of diabetogen toxicity disappear after 1<br>days, and suggesting that the damage may be owing to toxicity of<br>the diabetogen rather than diabetes itself. However,<br>many signs of diabetogen toxicity disappear after 14<br>days, and changes in experimental parameters are prob-<br>ably o the diabetogen rather than diabetes itself. However,<br>many signs of diabetogen toxicity disappear after 14<br>days, and changes in experimental parameters are prob-<br>ably owing to insulin deficiency itself as addition of<br>exogen many signs of diabetogen toxicity disappear after 14<br>days, and changes in experimental parameters are prob-<br>ably owing to insulin deficiency itself as addition of<br>exogenous insulin reverses these effects. Future work<br>must days, and changes in experiment<br>ably owing to insulin deficienc<br>exogenous insulin reverses thes<br>must unequivocally rule out chre<br>from the diabetogens themselves must unequivocally rule out chronic or delayed toxicity<br>from the diabetogens themselves.<br>**III. Diabetes and Cholesterol Metabolism** 

Cholesterol, a precursor for plasma membranes, bile III. Diabetes and Cholesterol Metabolism<br>Cholesterol, a precursor for plasma membranes, bile<br>salts, steroid hormones, and other molecules, circulates<br>in the plasma as part of various lipoprotein complexes, III. Diabetes and Cholesterol Metabolism<br>Cholesterol, a precursor for plasma membranes, bile<br>salts, steroid hormones, and other molecules, circulates<br>in the plasma as part of various lipoprotein complexes,<br>including chylom III. Diabetes and Cholesterol Metabolism<br>Cholesterol, a precursor for plasma membranes, bil<br>salts, steroid hormones, and other molecules, circulate<br>in the plasma as part of various lipoprotein complexes<br>including chylomicr Low density a precursor for plasma membranes, olle<br>
salts, steroid hormones, and other molecules, circulates<br>
in the plasma as part of various lipoprotein complexes,<br>
including chylomicrons, very low density lipoproteins,<br> in the plasma as part of various lipoprotein complexes,<br>including chylomicrons, very low density lipoproteins,<br>low density lipoproteins, and high density lipoproteins.<br>Hepatocytes are involved in synthesis and elimination including chylomicrons, very low density lipoproteins,<br>low density lipoproteins, and high density lipoproteins.<br>Hepatocytes are involved in synthesis and elimination of<br>cholesterol, both through cholesterol degradation int low density lipoproteins, and high density lipoproteins.<br>Hepatocytes are involved in synthesis and elimination of<br>cholesterol, both through cholesterol degradation into<br>bile acids and through cholesterol secretion into the **repaticyles are involved in synthesis and elimination of**<br>cholesterol, both through cholesterol degradation into<br>bile acids and through cholesterol secretion into the bile;<br>cholesterol is either reabsorbed from the intest bile acids and through cholesterol secretion into the bile; cholesterol is either reabsorbed from the intestines or 1988). creted in the feces. Hepatic synthesis of cholesterol is<br>ntrolled homeostatically by the level of dietary choles-<br>rol (Coleman and Rahman, 1992; Turley and Dietschy,<br>88).<br>Diabetics are prone to lipid disorders (Winocour et controlled homeostatically by the level of dietary cholesterol (Coleman and Rahman, 1992; Turley and Dietschy, 1988).<br>
1988).<br>
Diabetics are prone to lipid disorders (Winocour et al., 1992; Cairns and Peters, 1983; Gibbons

Diabetics are prone to lipid disorders (Winocour et al., 1992; Cairns and Peters, 1983; Gibbons, 1986), with atheroma accounting for 60 to 75% of deaths (Verges, 1991). Characteristic abnormalities in diabetics include 1992; Cairns and Peters, 1983; Gibbons, 1986), with<br>
1992; Cairns and Peters, 1983; Gibbons, 1986), with<br>
atheroma accounting for 60 to 75% of deaths (Verges,<br>
1991). Characteristic abnormalities in diabetics include<br>
decr 1992; Cairns and Peters, 1983; Gibbons, 1986), with<br>atheroma accounting for 60 to 75% of deaths (Verges,<br>1991). Characteristic abnormalities in diabetics include<br>decreased levels of high density lipoprotein cholesterol,<br>al atheroma accounting for 60 to 75% of deaths (Verges, 1991). Characteristic abnormalities in diabetics include decreased levels of high density lipoprotein cholesterol, along with increased mean plasma concentrations of cho 1991). Characteristic abnormalities in diabetics includ decreased levels of high density lipoprotein cholestero along with increased mean plasma concentrations (cholesterol, very low density lipoprotein, low densiti lipopr decreased levels of high density lipoprotein cholesterol,<br>along with increased mean plasma concentrations of<br>cholesterol, very low density lipoprotein, low density<br>lipoprotein, triglycerides (Barrett-Connor, 1992; Man-<br>zat along with increased mean plasma concentrations cholesterol, very low density lipoprotein, low densit<br>lipoprotein, triglycerides (Barrett-Connor, 1992; Man<br>zato et al., 1993; Verges, 1991), and apolipoprotein A-<br>and A-II ( cholesterol, very low density lipoprotein, low density<br>lipoprotein, triglycerides (Barrett-Connor, 1992; Man-<br>zato et al., 1993; Verges, 1991), and apolipoprotein A-I<br>and A-II (Taskinen et al., 1992). These effects are exa lipoprotein, triglycerides (Barrett-Connor, 1992; Man-<br>zato et al., 1993; Verges, 1991), and apolipoprotein A-I<br>and A-II (Taskinen et al., 1992). These effects are exac-<br>erbated by obesity (Laakso and Pyorala, 1990). How-<br> zato et al., 1993; Verges, 1991), and apolipoprotein A-I<br>and A-II (Taskinen et al., 1992). These effects are exac-<br>erbated by obesity (Laakso and Pyorala, 1990). How-<br>ever, a twin study (Dubrey et al., 1993) suggested that and A-II (Taskinen et al., 1992). These effects are exacerbated by obesity (Laakso and Pyorala, 1990). However, a twin study (Dubrey et al., 1993) suggested that there is no relationship between genetic susceptibility to i

DIABETES MELLITUS AND HEPATOBILLARY FUNCTION <sup>3</sup>

DIABETES MELLITUS AND HEP.<br>
lipids and lipoproteins, and two studies have shown St<br>
little correlation between lipoprotein (a) levels and dia-DIABETES MELLITUS AND<br>lipids and lipoproteins, and two studies have shown<br>little correlation between lipoprotein (a) levels and dia-<br>betic complications (Ritter et al., 1993; Winocour et al., DIABETES MELLITUS AND H<br>lipids and lipoproteins, and two studies have shown<br>little correlation between lipoprotein (a) levels and dia-<br>betic complications (Ritter et al., 1993; Winocour et al.,<br>1989). Nevertheless, there i lipids and lipoproteins, and two studies have shown Si<br>little correlation between lipoprotein (a) levels and dia-<br>betic complications (Ritter et al., 1993; Winocour et al., en<br>1989). Nevertheless, there is some evidence th lipids and lipoproteins, and two studies have shown St<br>little correlation between lipoprotein (a) levels and dia-<br>betic complications (Ritter et al., 1993; Winocour et al., er-<br>1989). Nevertheless, there is some evidence t little correlation between lipoprotein (a) levels and diabetic complications (Ritter et al., 1993; Winocour et al., 1989). Nevertheless, there is some evidence that activity of lipoprotein lipase is genetically determined betic complications (Ritter et al., 1993; Winocour et al., 1989). Nevertheless, there is some evidence that activity of lipoprotein lipase is genetically determined and is correlated with plasma triglyceride levels in diab 1989). Nevertheless, there is some evidence that activity vior<br>of lipoprotein lipase is genetically determined and is<br>correlated with plasma triglyceride levels in diabetics<br>(Ahn et al., 1993; Wilson et al., 1993). The li correlated with plasma triglyceride levels in diabetics<br>
(Ahn et al., 1993; Wilson et al., 1993). The lipid content<br>
of cell membranes seems to be disrupted by diabetes, as<br>
evidenced by increased nonenzymatic glycation, of cell membranes seems to be disrupted by diabetes, as<br>evidenced by increased nonenzymatic glycation, lipid<br>peroxidation, and cholesterol/phospholipid ratio (Watala<br>and Winocour, 1992).<br>Similar lipid anomalies occur in an

peroxidation, and cholesterol/phospholipid ratio (Watala port and Winocour, 1992).<br>
198<br>
Similar lipid anomalies occur in animal models as 199<br>
well. Tepperman et al. (1983) have shown a reduction in bloo<br>
the activity of and Winocour, 1992).<br>
Similar lipid anomalies occur in animal movell. Tepperman et al. (1983) have shown a reduce<br>
the activity of glycosyltransferases that are invo<br>
membrane glycoprotein synthesis in streptozotoc<br>
betic Similar lipid anomalies occur in animal models as 199<br>well. Tepperman et al. (1983) have shown a reduction in blow<br>the activity of glycosyltransferases that are involved in In<br>membrane glycoprotein synthesis in streptozoto well. Tepperman et al. (1983) have shown a reduction in block the activity of glycosyltransferases that are involved in In s membrane glycoprotein synthesis in streptozotocin-dia-<br>betic rats. Nonenzymatic glycosylation of the activity of glycosyltransferases that are involved in I<br>membrane glycoprotein synthesis in streptozotocin-dia-<br>betic rats. Nonenzymatic glycosylation of proteins is also<br>increased during diabetes in rats (Zimmerman, 19 membrane glycoprotein synthesis in streptozotocir<br>betic rats. Nonenzymatic glycosylation of proteins is<br>increased during diabetes in rats (Zimmerman, 198<br>diabetic rabbits, blood glucose is correlated posit<br>with beta-lipopr betic rats. Nonenzymatic glycosylation of proteins is also<br>increased during diabetes in rats (Zimmerman, 1989). In<br>diabetic rabbits, blood glucose is correlated positively<br>with beta-lipoprotein and negatively with alpha-li increased during diabetes in rats (Zimmerman, 1989). In diabetic rabbits, blood glucose is correlated positively with beta-lipoprotein and negatively with alpha-lipoprotein (Li et al., 1989), whereas hepatic lipoprotein fr mabetic raboits, blood glucose is correlated positively<br>with beta-lipoprotein and negatively with alpha-lipopro-<br>tein (Li et al., 1989), whereas hepatic lipoprotein frac-<br>tions are enriched with triacylglycerol (O'Meara et with beta-lipoprotein and negatively with alp<br>tein (Li et al., 1989), whereas hepatic lipopr<br>tions are enriched with triacylglycerol (O'M-<br>1991) and deficient in the major enzymes<br>cholesterol metabolism, hydroxymethylglu<br> **zyme A reductase, cholesterol (O'Meara et al.**<br>**291)** and deficient in the major enzymes regulating cholesterol metabolism, hydroxymethylglutaryl-coen zyme A reductase, cholesterol 7α-hydroxylase, and cho-<br>lesterol acylt 1991) and deficient in the major enzymes regulating gan cholesterol metabolism, hydroxymethylglutaryl-coen-<br>zyme A reductase, cholesterol  $7\alpha$ -hydroxylase, and cho-<br>lesterol acyltransferase (O'Meara et al., 1990). Mem-<br>b cholesterol metabolism, hydroxymethylglutaryl-co<br>zyme A reductase, cholesterol 7 $\alpha$ -hydroxylase, and c<br>lesterol acyltransferase (O'Meara et al., 1990). Me<br>brane fatty acid composition and fluidity are altered<br>diabetic ra zyme A reductase, choiesteror *ra*-hydroxylase, and cho-<br>lesterol acyltransferase (O'Meara et al., 1990). Mem-<br>brane fatty acid composition and fluidity are altered in<br>diabetic rats in liver (Venkatraman et al., 1991; Kord **in platelets** acylizanserase (O meara et al., 1990). Membrane fatty acid composition and fluidity are altered in diabetic rats in liver (Venkatraman et al., 1991; Kordowiak et al., 1990; Mimouni and Poisson, 1991), as wel orane ratty actd composite<br>
diabetic rats in liver (Venliak et al., 1990; Mimouni<br>
in platelets, aorta, and<br>
1992; Dang et al., 1988).<br>
Hepatic synthesis of c diabetic rats in iver (veinsatraman et al., 1991; Kordowisk et al., 1990; Mimouni and Poisson, 1991), as well as m<br>in platelets, aorta, and adipose cells (Egutkin et al., tl<br>1992; Dang et al., 1988).<br>Hepatic synthesis of c

in platelets, aorta, and adipose cells (Egutkin et al., the 1992; Dang et al., 1988). Ind Hepatic synthesis of cholesterol is increased more gal than two-fold in diabetic rats fed a high protein diet car (Kudchodkar et al. 1992; Dang et al., 1988). indicant reduction is increased more gal than two-fold in diabetic rats fed a high protein diet carr (Kudchodkar et al., 1988). However, insulin induces a systempid and significant reduction in bi repatic synthesis of cholesterol is increased more<br>than two-fold in diabetic rats fed a high protein diet<br>(Kudchodkar et al., 1988). However, insulin induces a<br>rapid and significant reduction in biliary lipid output in<br>dia (Kudchodkar et al., 1988). However, insulin induces a systems. Uptake of organic anions proceeds sodium inderapid and significant reduction in biliary lipid output in pendently (Potter et al., 1987) and is accelerated in t diabetic rats (Villanueva et al., 1990b), suggesting that insulin or its absence may play a role in mechanisms Several distinct, class-specific binding proteins in the<br>other than synthesis involved in the supply of biliary sinusoidal membrane of the hepatocyte probably repre-<br>lip msum or its absence may piay a rote in mechanisms<br>other than synthesis involved in the supply of biliary<br>lipids toward the canaliculi. Insulin deficiency decreases<br>the removal rates of triacylglycerols from the circula-<br>ti the removal rates of triacylglycerols from the liver as<br>well as the rate of their disappearance from the circula-<br>tion (Hirano et al., 1991; Moir and Zammit, 1992;<br>Redgrave and Callow, 1990; Roland and Maranhao,<br>1993; Yosh well as the rate of their disappearance from the circulawen as the rate of their disappearance from the circulation (Hirano et al., 1991; Moir and Zammit, 1992; Redgrave and Callow, 1990; Roland and Maranhao, 1993; Yoshino et al., 1990, 1992). In fact, chronic probucol therapy col therapy seems to normalize very low density lipoprotein composition, contributing to the accelerated removal of triglycerides from blood of streptozotocincol therapy seems to normalize very low density lipopro-<br>tein composition, contributing to the accelerated re-<br>in moval of triglycerides from blood of streptozotocin-<br>diabetic rats (Yoshino et al., 1991). Levels of trapoli **in alloxan diabetic rabbits, suggesting that insulin defi-**<br> **in alloxan diabetic rabbits, suggesting that insulin defi-**<br> **in alloxan diabetic rabbits, suggesting that insulin defi-**<br> **in alloxan diabetic rabbits, sugges** diabetic rats (Yoshino et al., 1991). Levels<br>apolipoprotein E messenger ribonucleic acid are red<br>in alloxan diabetic rabbits, suggesting that insulin o<br>ciency influences apolipoprotein E gene expression, t<br>decreasing hepat aponpoprotein E messenger rhonticleic actuater et al., in alloxan diabetic rabbits, suggesting that insulin defi-<br>ciency influences apolipoprotein E gene expression, thus<br>discussion that diabetes mellitus affects cholester ciency influences apolipoprotein E gene expression, thus<br>decreasing hepatic and adrenal cholesterol concentra-<br>tions (Lenich et al., 1991). It is clear from this limited hil<br>discussion that diabetes mellitus affects choles decreasing hepatic and adrenal cholesterol concentra-<br>tions (Lenich et al., 1991). It is clear from this limited<br>discussion that diabetes mellitus affects cholesterol pro-<br>duction and secretion by the liver for utilization tions (Lenich et al., 1991). It is clear from this limited discussion that diabetes mellitus affects cholesterol production and secretion by the liver for utilization by the body. Evaluations of additional details regardin tes, cholesterol homeostasis, and atherosclerosis appear elsewhere (Schwartz et al., 1992; Staprans et al., 1992;

DIABETES MELLITUS AND HEPATOBILIARY FUNCTION<br>
vo studies have shown Stern et al., 1992). The functional consequences of strep-<br>
otein (a) levels and dia-<br>
tozotocin-induced diabetes mellitus, with particular ref-EPATOBILIARY FUNCTION<br>
Stern et al., 1992). The functional consequences of strep-<br>
tozotocin-induced diabetes mellitus, with particular ref-<br>
erence to the cardiovascular system, were recently re-EPATOBILIARY FUNCTION 3<br>
Stern et al., 1992). The functional consequences of strep-<br>
tozotocin-induced diabetes mellitus, with particular ref-<br>
erence to the cardiovascular system, were recently re-<br>
viewed (Tomlinson et a Stern et al., 1992). The functional<br>tozotocin-induced diabetes mellitu<br>erence to the cardiovascular syst<br>viewed (Tomlinson et al., 1992). viewed (Tomlinson et al., 1992).<br>**IV. Diabetes and Hepatic Uptake** *A. General Considerations Regarding Hepatic Uptake*<br>*A. General Considerations Regarding Hepatic Uptake*<br>Bile acids, organic anions, and fatty acids are trans-

idenced by increased nonenzymatic glycation, lipid<br>
Sile acids, organic anions, and fatty acids are trans-<br>
Froxidation, and cholesterol/phospholipid ratio (Watala ported in blood largely bound to albumin (Berk et al.,<br>
19 the activity of glycosyltransferases that are involved in In spite of the very tight binding of most organic anions IV. Diabetes and Hepatic Uptake<br>General Considerations Regarding Hepatic Uptake<br>Bile acids, organic anions, and fatty acids are trans-<br>rted in blood largely bound to albumin (Berk et a ported in blood largely bound to albumin (Berk et al., A. General Considerations Regarding Hepatic Uptake<br>Bile acids, organic anions, and fatty acids are trans-<br>ported in blood largely bound to albumin (Berk et al.,<br>1987; Meijer and van der Sluijs, 1989; Sorrentino et al.,<br>199 A. General Considerations Regaraing Hepatic Uptake<br>
Bile acids, organic anions, and fatty acids are trans-<br>
ported in blood largely bound to albumin (Berk et al.,<br>
1987; Meijer and van der Sluijs, 1989; Sorrentino et al.,<br> Bile acids, organic anions, and fatty acids are transported in blood largely bound to albumin (Berk et al., 1987; Meijer and van der Sluijs, 1989; Sorrentino et al., 1990), and hepatic extraction of bile acids from portal ported in blood largely bound to albumin (Berk et al., 1987; Meijer and van der Sluijs, 1989; Sorrentino et al., 1990), and hepatic extraction of bile acids from portal blood plasma is extremely efficient (Aldini et al., 1 1987; Meijer and van der Sluijs, 1989; Sorrentino et al., 1990), and hepatic extraction of bile acids from portal<br>blood plasma is extremely efficient (Aldini et al., 1982).<br>In spite of the very tight binding of most organi 1990), and hepatic extraction of bile acids from portal<br>blood plasma is extremely efficient (Aldini et al., 1982).<br>In spite of the very tight binding of most organic anions<br>to albumin, uptake is preceded by dissociation of blood plasma is extremely efficient (Aldini et al., 1983).<br>In spite of the very tight binding of most organic anio<br>to albumin, uptake is preceded by dissociation of the<br>ligand-albumin complex, because hepatic extraction<br>al In spite of the very tight binding of most organic anion<br>to albumin, uptake is preceded by dissociation of th<br>ligand-albumin complex, because hepatic extraction o<br>albumin is negligible (Berk et al., 1987). In vivo obser<br>va to albumin, uptake is preceded by dissociation of the ligand-albumin complex, because hepatic extraction of albumin is negligible (Berk et al., 1987). In vivo observations (Bloomer et al., 1973) led to the concept of "surf ligand-albumin complex, because hepatic extraction of<br>albumin is negligible (Berk et al., 1987). In vivo obser-<br>vations (Bloomer et al., 1973) led to the concept of "sur-<br>face-mediated dissociation" and the existence of a albumin is negligible (Berk et al., 1987). In vivo of vations (Bloomer et al., 1973) led to the concept of 'face-mediated dissociation" and the existence of a cific albumin-receptor on the sinusoidal plamembrane, which fac vations (Bloomer et al., 1973) led to the concept of "surface-mediated dissociation" and the existence of a specific albumin receptor on the sinusoidal plasma<br>membrane, which facilitates dissociation of albumin-or-<br>ganic a face-mediated dissociation" and the existence of a specific albumin receptor on the sinusoidal plasma<br>membrane, which facilitates dissociation of albumin-or-<br>ganic anion complexes (Ockner et al., 1983). Although<br>the exact cific albumin receptor on the sinusoidal pla<br>membrane, which facilitates dissociation of albumin<br>ganic anion complexes (Ockner et al., 1983). Althe<br>the exact nature of this (nonspecific) interaction rem<br>unclear, surface-me membrane, which facilitates dissociation of albumin-organic anion complexes (Ockner et al., 1983). Although the exact nature of this (nonspecific) interaction remains unclear, surface-mediated facilitation of albumin-organ ganic anion complexes (Ockner et al., 1983). Although<br>the exact nature of this (nonspecific) interaction remains<br>unclear, surface-mediated facilitation of albumin-or-<br>ganic anion dissociation probably plays a role in hepat e exact nature of this (nonspecific) interaction remaindear, surface-mediated facilitation of albuminimic anion dissociation probably plays a role in heps take processes in vivo.<br>As extensively reviewed elsewhere (Berk and

unclear, surface-mediated facilitation of albumin-or-<br>ganic anion dissociation probably plays a role in hepatic<br>uptake processes in vivo.<br>As extensively reviewed elsewhere (Berk and Strem-<br>mel, 1986; Berk et al., 1987; Kui ganic anion dissociation probably plays a role in hepatic<br>uptake processes in vivo.<br>As extensively reviewed elsewhere (Berk and Strem-<br>mel, 1986; Berk et al., 1987; Kuipers and Vonk, 1991),<br>the hepatic uptake of organic an uptake processes in vivo.<br>
As extensively reviewed elsewhere (Berk and Strem-<br>
mel, 1986; Berk et al., 1987; Kuipers and Vonk, 1991)<br>
the hepatic uptake of organic anions such as bilirubin<br>
indocyanine green, sulfobromopht As extensively reviewed elsewhere (Berk and Strem-<br>mel, 1986; Berk et al., 1987; Kuipers and Vonk, 1991),<br>the hepatic uptake of organic anions such as bilirubin,<br>indocyanine green, sulfobromophthalein and rose ben-<br>gal has the hepatic uptake of organic anions such as bilirubin,<br>indocyanine green, sulfobromophthalein and rose ben-<br>gal has been shown to meet the kinetic criteria for<br>carrier-mediated transport in a variety of experimental the hepatic uptake of organic anions such as bilirubin<br>indocyanine green, sulfobromophthalein and rose ben<br>gal has been shown to meet the kinetic criteria fo<br>carrier-mediated transport in a variety of experiments<br>systems. indocyanine green, sulfobromophthalein and rose bengal has been shown to meet the kinetic criteria for carrier-mediated transport in a variety of experimental systems. Uptake of organic anions proceeds sodium independently gal has been shown to meet the kinetic criteria for carrier-mediated transport in a variety of experimental systems. Uptake of organic anions proceeds sodium independently (Potter et al., 1987) and is accelerated in the pr rrier-mediated transport in a variety of experimental<br>stems. Uptake of organic anions proceeds sodium inde-<br>ndently (Potter et al., 1987) and is accelerated in the<br>esence of chloride (Min et al., 1990; Wolkoff et al., 1987 systems. Uptake of organic anions proceeds sodium inc<br>pendently (Potter et al., 1987) and is accelerated in t<br>presence of chloride (Min et al., 1990; Wolkoff et al., 198<br>Several distinct, class-specific binding proteins in

col therapy seems to normalize very low density lipopro-<br>tein composition, contributing to the accelerated re-<br>moval of triglycerides from blood of streptozotocin-<br>diabetic rats (Yoshino et al., 1991). Levels of transport pendently (Potter et al., 1987) and is accelerated in the<br>presence of chloride (Min et al., 1990; Wolkoff et al., 1987).<br>Several distinct, class-specific binding proteins in the<br>sinusoidal membrane of the hepatocyte probab presence of chloride (Min et al., 1990; Wolkoff et al., 1987).<br>Several distinct, class-specific binding proteins in the<br>sinusoidal membrane of the hepatocyte probably repre-<br>sent separate uptake systems for different class Several distinct, class-specific binding proteins in the<br>sinusoidal membrane of the hepatocyte probably repre-<br>sent separate uptake systems for different classes of<br>negatively charged compounds, i.e., for organic anions,<br>b sinusoidal membrane of the hepatocyte probably repre<br>sent separate uptake systems for different classes o<br>negatively charged compounds, i.e., for organic anions<br>bile acids, and fatty acids. For example, a 107 kD proteir<br>c sent separate uptake systems for different classes of<br>negatively charged compounds, i.e., for organic anions,<br>bile acids, and fatty acids. For example, a 107 kD protein<br>called bilitranslocase was reported to consist of tw negatively charged compounds, i.e., for organic anions,<br>bile acids, and fatty acids. For example, a 107 kD protein<br>called bilitranslocase was reported to consist of two non-<br>identical subunits ( $\alpha = 37$  kD,  $\beta = 35.5$  kD) bile acids, and fatty acids. For example, a 107 kD protein<br>called bilitranslocase was reported to consist of two non-<br>identical subunits ( $\alpha = 37$  kD,  $\beta = 35.5$  kD) with a<br>subunit composition of  $\alpha_2\beta$  (Lunazzi et al., called bilitranslocase was reported to consist of two non-<br>identical subunits ( $\alpha = 37$  kD,  $\beta = 35.5$  kD) with a<br>subunit composition of  $\alpha_2\beta$  (Lunazzi et al., 1982). An<br>antibody to bilitranslocase inhibited bilirubin identical subunits ( $\alpha = 37$  kD,  $\beta = 35.5$  kD) with subunit composition of  $\alpha_2\beta$  (Lunazzi et al., 1982). A antibody to bilitranslocase inhibited bilirubin transport in the isolated perfused rat liver and insertion of subunit composition of  $\alpha_2\beta$  (Lunazzi et al., 1982). A<br>antibody to bilitranslocase inhibited bilirubin transpo<br>in the isolated perfused rat liver and insertion of th<br>protein in liposomes reconstituted sulfobromophthale antibody to bilitranslocase inhibited bilirubin transport<br>in the isolated perfused rat liver and insertion of the<br>protein in liposomes reconstituted sulfobromophthalein<br>transport (Sottocasa et al., 1982). Also, a 55 kD sul in the isolated perfused rat liver and insertion of the protein in liposomes reconstituted sulfobromophthalein<br>transport (Sottocasa et al., 1982). Also, a 55 kD sulfo-<br>bromophthalein and bilirubin binding protein was iso-<br> protein in liposomes reconstituted sulfobromophthalein<br>transport (Sottocasa et al., 1982). Also, a 55 kD sulfo-<br>bromophthalein and bilirubin binding protein was iso-<br>lated from a rat liver plasma membrane fraction en-<br>rich transport (Sottocasa et al., 1982). Also, a 55 kD sulfo-<br>bromophthalein and bilirubin binding protein was iso-<br>lated from a rat liver plasma membrane fraction en-<br>riched in basolateral domains (Stremmel et al., 1983).<br>Mono bromophthalein and bilirubin binding protein was isolated from a rat liver plasma membrane fraction enriched in basolateral domains (Stremmel et al., 1983).<br>Monospecific antibodies raised against this protein in-<br>hibited t lated from a rat liver plasma membrane fraction en-<br>riched in basolateral domains (Stremmel et al., 1983).<br>Monospecific antibodies raised against this protein in-<br>hibited the uptake of sulfobromophthalein and bilirubin<br>by riched in basolateral domains (Stremmel et al., 1983).<br>Monospecific antibodies raised against this protein in-<br>hibited the uptake of sulfobromophthalein and bilirubin<br>by freshly isolated rat hepatocytes (Stremmel and Berk, by freshly isolated rat hepatocytes (Stremmel and Berk, hibited the uptake of sulfobromophthalein and bilirubin<br>by freshly isolated rat hepatocytes (Stremmel and Berk,<br>1986) and by Hep G2 human hepatoma cells (Stremmel<br>and Diede, 1990). Using somewhat different methodol-<br>ogy, a by freshly isolated rat hepatocytes (Stremmel and Berk, 1986) and by Hep G2 human hepatoma cells (Stremmel and Diede, 1990). Using somewhat different methodology, an organic anion binding protein was isolated from rat live

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4<br>1980) with similar molecular weight and binding char-<br>acteristics. acteristics.

**At least three different mechanisms are involved in**<br> **At least three different mechanisms are involved in**<br>
the basolateral uptake of bile acids into rat hepatocytes: sinu<br>
(a) a Na<sup>+</sup>-independent carrier-mediated proces (a)) 1980) with similar molecular weight and binding characteristics.<br>
At least three different mechanisms are involved in teritie basolateral uptake of bile acids into rat hepatocytes: since (a) a Na<sup>+</sup>-independent carri At least three different mechanisms are involved in the basolateral uptake of bile acids into rat hepatocytes:  $(a)$  a Na<sup>+</sup>-independent carrier-mediated process,  $(b)$  a pNa<sup>+</sup>-dependent bile acid uptake system, and  $(c)$  n the basolateral uptake of bile acids into rat hepatocytes:<br>  $(a)$  a Na<sup>+</sup>-independent carrier-mediated process,  $(b)$  a<br>
Na<sup>+</sup>-dependent bile acid uptake system, and  $(c)$  nonionic<br>
diffusion followed by intracellular bindin (a) a Na<sup>+</sup>-independent carrier-mediated process, (b) a port systems with similar molecular weights on sodium Na<sup>+</sup>-dependent bile acid uptake system, and (c) nonionic dodecylsulfate-gel electrophoresis.<br>diffusion followe **Meier et a!., 1984). The saturable, carrier-mediated,**  $Na<sup>+</sup>$ -independent uptake may occur for certain bile acid derivatives including cholate, glycocholate and glycocheproteins and amidation with taurine or glycine or c<br>jugation with sulfate or glucuronidate (Meier, 19<br>Meier et al., 1984). The saturable, carrier-mediat<br>Na<sup>+</sup>-independent uptake may occur for certain bile a<br>derivatives inc jugation with sulfate or glucuronidate (Meier, 1991;<br>Meier et al., 1984). The saturable, carrier-mediated,<br>Na<sup>+</sup>-independent uptake may occur for certain bile acid<br>derivatives including cholate, glycocholate and glycoche-<br> Meier et al., 1984). The saturable, carrier-mediated,<br>Na<sup>+</sup>-independent uptake may occur for certain bile acid<br>derivatives including cholate, glycocholate and glycoche-<br>nodeoxycholate (Van Dyke et al., 1982). More importa  $Na^+$ -independent uptake may occur for certain bile acid<br>derivatives including cholate, glycocholate and glycoche-<br>nodeoxycholate (Van Dyke et al., 1982). More important<br>quantitatively, the electrogenic basolateral  $Na^+/bile$ derivatives including cholate, glycocholate and glycocholate nodeoxycholate (Van Dyke et al., 1982). More importan quantitatively, the electrogenic basolateral Na<sup>+</sup>/bile acid cotransport system moves trihydroxy conjugated nodeoxycholate (Van Dyke et al., 1982). More importan<br>quantitatively, the electrogenic basolateral Na<sup>+</sup>/bil<br>acid cotransport system moves trihydroxy conjugate<br>bile salts such as taurocholate. The hepatocellula<br>Na<sup>+</sup>/bile quantitatively, the electrogenic basolateral Na<sup>+</sup>/bile the acid cotransport system moves trihydroxy conjugated by bile salts such as taurocholate. The hepatocellular AdMa<sup>+</sup>/bile acid uptake system has broad substrate sp acid cotransport system moves trihydroxy conjugated<br>bile salts such as taurocholate. The hepatocellular<br> $Na^+/$ bile acid uptake system has broad substrate spec-<br>ificity, and possible cosubstrates include steroids and<br>steroi bile salts such as taurocholate. The hepatocellular Additional details of the hepatic uptake of organic cat-<br>Na<sup>+</sup>/bile acid uptake system has broad substrate spec-<br>ificity, and possible cosubstrates include steroids and Na<sup>+</sup>/bile acid uptake system has broad substrate spec-<br>ificity, and possible cosubstrates include steroids and<br>isteroid metabolites, cyclic oligopeptides, and numerous<br>drugs. The Na<sup>+</sup>/bile acid cotransport system starts ificity, and possible cosubstrates include steroids and in<br>steroid metabolites, cyclic oligopeptides, and numerous<br>drugs. The Na<sup>+</sup>/bile acid cotransport system starts to be<br> $B$ .<br>expressed on the basolateral membrane at l steroid metabolites, cyclic oligopeptides, and numerous<br>drugs. The Na<sup>+</sup>/bile acid cotransport system starts to be<br>expressed on the basolateral membrane at late gestation<br>in rodents (fetal days 16 to 20) and reaches > 90% artigs. The Na 7 bile acid cotrainsport system starts to be<br>expressed on the basolateral membrane at late gestation<br>in rodents (fetal days 16 to 20) and reaches > 90% of the<br>and Levy, 1990). Transport function is associate in rodents (fetal days 16 to 20) and reaches  $> 90\%$  of the adult level approximately 28 days after birth (Von Dippe and Levy, 1990). Transport function is associated with a 48 to 49 kD protein (Ananthanarayanan et al., and Levy, 1990). Transport function is associated with a and Levy, 1990). Transport function is associated with a<br>48 to 49 kD protein (Ananthanarayanan et al., 1988). to<br>Na<sup>+</sup>-dependent taurocholate uptake has been expressed S<br>in *Xenopus laevis* oocytes (Hagenbuch et al., 1990 48 to 49 kD protein (Ananthanarayanan et al., 1988)  $Na^+$ -dependent taurocholate uptake has been expressee in *Xenopus laevis* occytes (Hagenbuch et al., 1990). Finally, the carrier might actually exist as a trimeric of t ma -aependent taurocholate uptake has been expressed<br>in Xenopus laevis oocytes (Hagenbuch et al., 1990). Fi<br>nally, the carrier might actually exist as a trimeric of<br>tetrameric aggregate in the plasma membrane, inas<br>much as many, the carrier imght actually exist as a trimeric or (Centerameric aggregate in the plasma membrane, inas-<br>much as recent radiation inactivation data have suggested a minimal functional molecular mass of the Na<sup>+</sup>- by<br>c much as recent radiation inactivation data have sug-<br>gested a minimal functional molecular mass of the Na<sup>+</sup>-<br>coupled bile acid uptake system of 170 kD (Elsner and<br>Ziegler, 1989). Cloning and sequencing of this important<br>h gested a minimal functional molecular m<br>coupled bile acid uptake system of 170 l<br>Ziegler, 1989). Cloning and sequencing of<br>hepatocellular bile acid transporting pol<br>rently in progress in several laboratories<br>Finally, undis upled bile acid uptake system of 170 kD (Elsner and al.<br>egler, 1989). Cloning and sequencing of this important tat<br>patocellular bile acid transporting polypeptide is cur-<br>bis<br>muly in progress in several laboratories. Trina

Ziegler, 1989). Cloning and sequencing of this important<br>hepatocellular bile acid transporting polypeptide is cur-<br>rently in progress in several laboratories.<br>Finally, undissociated (protonated) unconjugated bile<br>acids are hepatocellular bile acid transporting polypeptide is currently in progress in several laboratories.<br>
Finally, undissociated (protonated) unconjugated bile<br>
acids are especially prone to diffuse passively across<br>
biological rently in progress in several laboratories.<br>Finally, undissociated (protonated) unconjugated bile<br>acids are especially prone to diffuse passively across<br>biological membranes. Nonsaturable uptake by nonionic<br>diffusion is de Finally, undissociated (protonated) unconjugated l<br>acids are especially prone to diffuse passively acr<br>biological membranes. Nonsaturable uptake by nonic<br>diffusion is definitely relevant for certain hydropho<br>bile acids suc biological membranes. Nonsaturable uptake by nonionic<br>diffusion is definitely relevant for certain hydrophobic<br>bile acids such as ursodeoxycholic and other unconju-<br>gated mono- and dihydroxy bile acids (Lake et al., 1988), diffusion is definitely relevant for certain hydrophobic<br>bile acids such as ursodeoxycholic and other unconju-<br>gated mono- and dihydroxy bile acids (Lake et al., 1988),<br>and may also occur for more water-soluble unconjugate diffusion is definitely relevant for certain hydrophologie acids such as ursodeoxycholic and other uncongated mono- and dihydroxy bile acids (Lake et al., 198 and may also occur for more water-soluble unconjugat bile acids bile acids such as ursodeoxycholic and other unconju-<br>gated mono- and dihydroxy bile acids (Lake et al., 1988), streptozotocin (Ooi et al., 1992).<br>and may also occur for more water-soluble unconjugated Lack of insulin in d gated mono- and dihydroxy bile acids (Lake et al., 1988), strepto<br>and may also occur for more water-soluble unconjugated Lack<br>bile acids such as cholic acid (Caflisch et al., 1990). animal<br>The isolation of specific bindin

and may also occur for more water-soluble unconjubile acids such as cholic acid (Caflisch et al., 199<br>The isolation of specific binding proteins exh<br>transport functions for organic anions, which difference described for b those described for bile acids  $(\sim 48 \text{ kD})$  (Ananthanarayanan et al., 1988) and for fatty acids  $(\sim 40 \text{ kD})$  (Stremmel et al., 1985), provides evidence that there are separate The isolation of specific binding proteins exhibiting<br>transport functions for organic anions, which differ from<br>those described for bile acids  $(\sim 48 \text{ kD})$  (Ananthanaray-<br>anan et al., 1988) and for fatty acids  $(\sim 40 \text{ k$ transport functions for organic anions, which differ from<br>those described for bile acids  $(\sim 48 \text{ kD})$  (Ananthanaray-<br>anan et al., 1988) and for fatty acids  $(\sim 40 \text{ kD})$  (Stremmel<br>et al., 1985), provides evidence that th those described for bile acids  $(\sim 48 \text{ kD})$  (Ananthanaray-<br>anan et al., 1988) and for fatty acids  $(\sim 40 \text{ kD})$  (Stremmel<br>et al., 1985), provides evidence that there are separate<br>uptake systems for different classes of n anan et al., 1988) and for fatty acids  $(\sim 40 \text{ kD})$  (Stremme<br>et al., 1985), provides evidence that there are separat<br>uptake systems for different classes of negatively<br>charged compounds. Reported interactions between or<br> et al., 1985), provides evidence that there are separate<br>uptake systems for different classes of negatively<br>charged compounds. Reported interactions between or-<br>ganic anions and bile acids and a variety of other com-<br>pound uptake systems for different classes of negatively<br>charged compounds. Reported interactions between or-<br>ganic anions and bile acids and a variety of other com-<br>pounds in various studies suggest that two transport<br>systems e charged compounds. Reported interactions between organic anions and bile acids and a variety of other compounds in various studies suggest that two transport systems exist with overlapping substrate specificities (Buscher ganic anions and bile acids and a variety of other compounds in various studies suggest that two transport systems exist with overlapping substrate specificities (Buscher et al., 1986; Frimmer and Ziegler, 1988; Meijer et pounds in various studies suggest that two transport rosystems exist with overlapping substrate specificities rat (Buscher et al., 1986; Frimmer and Ziegler, 1988; Meijer inset al., 1990; Petzinger et al., 1987; Zimmerli e systems exist with overlapping substrate specificities rate.<br>
(Buscher et al., 1986; Frimmer and Ziegler, 1988; Meijer ins<br>
et al., 1990; Petzinger et al., 1987; Zimmerli et al., 1989). tra<br>
Further studies are needed to d

FORTH SANDERS<br>the Na<sup>+</sup>-independent anion system is the 55 kD protein.<br>However, as long as the proteins have not been charac-EXAMPERS<br>
the Na<sup>+</sup>-independent anion system is the 55 kD prote<br>
However, as long as the proteins have not been char<br>
terized, one can not exclude the possibility that t FORTHERS<br>the Na<sup>+</sup>-independent anion system is the 55 kD protein.<br>However, as long as the proteins have not been charac-<br>terized, one can not exclude the possibility that the<br>sinusoidal membrane contains multiple distinct the Na<sup>+</sup>-independent anion system is the 55 kD protein However, as long as the proteins have not been charaterized, one can not exclude the possibility that the sinusoidal membrane contains multiple distinct transport sys the Na<sup>+</sup>-independent anion system is the 55 kD protein.<br>However, as long as the proteins have not been characterized, one can not exclude the possibility that the<br>sinusoidal membrane contains multiple distinct trans-<br>port However, as long as the protein<br>terized, one can not exclude t<br>sinusoidal membrane contains<br>port systems with similar molec<br>dodecylsulfate-gel electrophores<br>At least two distinct uptake sy **At least two distinct the possibility that the sinusoidal membrane contains multiple distinct transport systems with similar molecular weights on sodium dodecylsulfate-gel electrophoresis.<br>At least two distinct uptake sys** 

port systems with similar molecular weights on sodium<br>dodecylsulfate-gel electrophoresis.<br>At least two distinct uptake systems transport organic<br>cations and have separate, albeit overlapping, substrate<br>specificities (Neef dodecylsulfate-gel electrophoresis.<br>At least two distinct uptake systems transport organic<br>cations and have separate, albeit overlapping, substrate<br>specificities (Neef et al., 1984a,b; Mol and Meijer, 1990;<br>Steen and Meije At least two distinct uptake systems transport organic<br>cations and have separate, albeit overlapping, substrate<br>specificities (Neef et al., 1984a,b; Mol and Meijer, 1990;<br>Steen and Meijer, 1991). The monovalent cation car specificities (Neef et al., 1984a,b; Mol and Meijer, 1990;<br>Steen and Meijer, 1991). The monovalent cation carrier<br>is an energy-requiring,  $Na^+$ -independent system that is<br>not inhibited by ouabain or taurocholate but stron Steen and Meijer, 1991). The monovalent cation carrier<br>is an energy-requiring,  $Na^+$ -independent system that is<br>not inhibited by ouabain or taurocholate but strongly<br>blocked by sulfhydryl reagents and choline. Uptake of<br>t is an energy-requiring,  $Na^+$ -independent system that is not inhibited by ouabain or taurocholate but strongly not inhibited by ouabain or taurocholate but strongly<br>blocked by sulfhydryl reagents and choline. Uptake of<br>the more lipophilic bivalent cations is strongly inhibited<br>by ouabain and taurocholate and unaffected by choline.<br> blocked by sulfhydryl reagents and choline. Uptake the more lipophilic bivalent cations is strongly inhibite by ouabain and taurocholate and unaffected by choline Additional details of the hepatic uptake of organic cations the more lipophilic bivalent cations is strongly<br>by ouabain and taurocholate and unaffected h<br>Additional details of the hepatic uptake of or<br>ions may be found in other reviews (Meijer, 1<br>inger et al., 1989a; Stein and Meij *B. Effects of Insulin and Insulin Deficiency on*<br>*B. Effects of Insulin and Insulin Deficiency on*<br>*Hepatic Uptake*<br>The direct influence of insulin on hepatic protein

adult level approximately 28 days after birth (Von Dippe thesis may be felt both by the enzymes involved in he-<br>and Levy, 1990). Transport function is associated with a patic biotransformation and by the protein carriers ger et al., 1989a; Stein and Meijer, 1991).<br> *Effects of Insulin and Insulin Deficiency on*<br> *epatic Uptake*<br>
The direct influence of insulin on hepatic protein syn-<br>
esis may be felt both by the enzymes involved in he-B. Effects of Insulin and Insulin Deficiency on<br>Hepatic Uptake<br>The direct influence of insulin on hepatic protein syn-<br>thesis may be felt both by the enzymes involved in he-<br>patic biotransformation and by the protein carri partic Uptake<br>
Hepatic Uptake<br>
The direct influence of insulin on hepatic protein syn-<br>
thesis may be felt both by the enzymes involved in he-<br>
patic biotransformation and by the protein carriers con-<br>
trolling hepatic upt The direct influence of insulin on hepatic protein syn-<br>thesis may be felt both by the enzymes involved in he-<br>patic biotransformation and by the protein carriers con-<br>trolling hepatic uptake and canalicular secretion.<br>Sev The direct influence of insulin on hepatic protein synthesis may be felt both by the enzymes involved in hepatic biotransformation and by the protein carriers controlling hepatic uptake and canalicular secretion.<br>Several s thesis may be felt both by the enzymes involved in hepatic biotransformation and by the protein carriers controlling hepatic uptake and canalicular secretion.<br>Several studies suggest that synthesis of some hepatic proteins patic biotransformation and by the protein carriers controlling hepatic uptake and canalicular secretion.<br>Several studies suggest that synthesis of some hepatic<br>proteins is also affected by insulin-dependent diabetes<br>(Cedo trolling hepatic uptake and canalicular secretion.<br>Several studies suggest that synthesis of some hepatic<br>proteins is also affected by insulin-dependent diabetes<br>(Cedola et al., 1975; Ingebretson et al., 1972; Jefferson,<br>1 Several studies suggest that synthesis of some hepatic proteins is also affected by insulin-dependent diabetes (Cedola et al., 1975; Ingebretson et al., 1972; Jefferson, 1980; Jefferson et al., 1983; Pain and Garlick, 197 proteins is also affected by insulin-dependent diabetes (Cedola et al., 1975; Ingebretson et al., 1972; Jefferson, 1980; Jefferson et al., 1983; Pain and Garlick, 1974). Enzymes whose activities are affected by insulin tr (Cedola et al., 1975; Ingebretson et al., 1972; Jefferson, 1980; Jefferson et al., 1983; Pain and Garlick, 1974). Enzymes whose activities are affected by insulin treatment or by diabetes include  $\gamma$ -cystathionase, cys-<br> 1980; Jefferson et al., 1983; Pain and Garlick, 1974). Enzymes whose activities are affected by insulin treatment or by diabetes include  $\gamma$ -glutamylcysteine synthetase (Lu et al., 1992), tyrosine aminotransferase,  $\gamma$ zymes whose activities are affected by insulin treatmer<br>by diabetes include  $\gamma$ -glutamylcysteine synthetase (L<br>al., 1992), tyrosine aminotransferase,  $\gamma$ -cystathionase,<br>tathionine  $\beta$ -synthase (Hargrove et al., 1989), by diabetes include  $\gamma$ -glutamylcysteine synthetase (Lu et al., 1992), tyrosine aminotransferase,  $\gamma$ -cystathionase, cystathionine  $\beta$ -synthase (Hargrove et al., 1989), fructose-1,6-bisphosphatase (Jiminez-Jativa et al al., 1992), tyrosine aminotransierase, γ-cystatinonase, cystathionine β-synthase (Hargrove et al., 1989), fructose-1,6-<br>bisphosphatase (Jiminez-Jativa et al., 1992), γ-glutamyl-<br>transpeptidase (Vacek et al., 1990; Watkins bisphosphatase (Jiminez-Jativa et al., 1992),  $\gamma$ -glutamyl-<br>transpeptidase (Vacek et al., 1990; Watkins and Smith,<br>1993), Na<sup>+</sup>-K<sup>+</sup>-ATPase (Carnovale et al., 1991) and serine<br>proteinase (Guenet et al., 1989). In additio transpeptidase (Vacek et al., 1990; Watkins and Smith, 1993), Na<sup>+</sup>-K<sup>+</sup>-ATPase (Carnovale et al., 1991) and serine proteinase (Guenet et al., 1989). In addition, hepatic concentrations of insulin-like growth factor-bindin 1993), Na<sup>+</sup>-K<sup>+</sup>-ATPase (Carnovale et al., 1991) and serine<br>proteinase (Guenet et al., 1989). In addition, hepatic con-<br>centrations of insulin-like growth factor-binding protein-1<br>can be decreased by administration of ex centrations of insulin-like growth factor-binding protein-1<br>can be decreased by administration of exogenous insulin<br>and be increased by induction of diabetes in rats with<br>streptozotocin (Ooi et al., 1992).<br>Lack of insulin can be decreased by administration of exogenous insulin

can be decreased by administration of exogenous insuline<br>and be increased by induction of diabetes in rats with<br>streptozotocin (Ooi et al., 1992).<br>Lack of insulin in diabetic humans and experimental<br>animals may have pronou and be increased by induction of diabetes in rats with<br>streptozotocin (Ooi et al., 1992).<br>Lack of insulin in diabetic humans and experimenta<br>animals may have pronounced effects on hepatic uptake<br>of chemicals, drug biotrans streptozotocin (Ooi et al., 1992).<br>Lack of insulin in diabetic humans and experimental<br>animals may have pronounced effects on hepatic uptake<br>of chemicals, drug biotransformation, and subsequent<br>biliary excretion. For examp Lack of insulin in diabetic humans and experimental<br>animals may have pronounced effects on hepatic uptake<br>of chemicals, drug biotransformation, and subsequent<br>biliary excretion. For example, the rate of uptake of<br>isoniazid of chemicals, drug biotransformation, and subsequent biliary excretion. For example, the rate of uptake of isoniazid into liver, lung, diaphragm and brain is enhanced in the presence of insulin, but the mechanism of chemicals, drug biotransformation, and subsequent<br>biliary excretion. For example, the rate of uptake of<br>isoniazid into liver, lung, diaphragm and brain is en-<br>hanced in the presence of insulin, but the mechanism<br>has yet biliary excretion. For example, the rate of uptake of isoniazid into liver, lung, diaphragm and brain is enhanced in the presence of insulin, but the mechanism has yet to be elucidated (Danysz and Wisniewski, 1965; Wisniew isoniazid into liver, lung, diaphragm and brain is enhanced in the presence of insulin, but the mechanism<br>has yet to be elucidated (Danysz and Wisniewski, 1965;<br>Wisniewski, 1968). Dodeur and coworkers (1982) assert<br>that th hanced in the presence of insulin, but the mechani<br>has yet to be elucidated (Danysz and Wisniewski, 19<br>Wisniewski, 1968). Dodeur and coworkers (1982) ass<br>that the diabetes-induced impairment of binding prot<br>is responsible has yet to be elucidated (Danysz and Wisniewski, 1968). Wisniewski, 1968). Dodeur and coworkers (1982) asset<br>that the diabetes-induced impairment of binding proteination-diabetic is responsible for a 50% decrease in the up Wisniewski, 1968). Dodeur and coworkers (1982) assert<br>that the diabetes-induced impairment of binding protein<br>is responsible for a 50% decrease in the uptake of asialoo-<br>rosomucoid by hepatocytes from streptozotocin-diabet that the diabetes-induced impairment of binding protein<br>is responsible for a 50% decrease in the uptake of asialoo-<br>rosomucoid by hepatocytes from streptozotocin-diabetic<br>rats. Future studies will need to determine whether is responsible for a 50% decrease in the uptake<br>rosomucoid by hepatocytes from streptozotoc<br>rats. Future studies will need to determine whe<br>insulin injection directly affects the synthesi<br>transport proteins involved in hep somucoid by hepatocytes from streptozotocin-diabetic<br>ts. Future studies will need to determine whether or not<br>sulin injection directly affects the synthesis of those<br>ansport proteins involved in hepatic uptake.<br>Diabetes al rats. Future studies will need to determine whether or not<br>insulin injection directly affects the synthesis of those<br>transport proteins involved in hepatic uptake.<br>Diabetes also affects the balance of electrolytes and<br>thei

**a**spet

# **V. Diabetes** and **Biotransformation**

Na<sup>+</sup>, K<sup>+</sup>, and bicarbonate ions. These disruptions may<br>influence either the uptake (Erlinger, 1982; Schar-<br>schmidt et al., 1975) or excretion (Watkins and Noda,<br>1986) of Na<sup>+</sup>-dependent chemicals. Increases in the size<br> Na', K', and bicarbonate ions. These disruptions may<br>influence either the uptake (Erlinger, 1982; Schar-<br>schmidt et al., 1975) or excretion (Watkins and Noda,<br>1986) of Na<sup>+</sup>-dependent chemicals. Increases in the size<br>of th influence either the uptake (Erlinger, 1982; Schar-<br>schmidt et al., 1975) or excretion (Watkins and Noda,<br>1986) of Na<sup>+</sup>-dependent chemicals. Increases in the size<br>of the bile acid pool in diabetic rats may also influence schmidt et al., 1975) or excretion (Watkins and Noda, 1986) of Na<sup>+</sup>-dependent chemicals. Increases in the size of the bile acid pool in diabetic rats may also influence uptake. For example, the disappearance of rose benga 1986) of Na<sup>+</sup>-dependent chemicals. Increases in the size<br>of the bile acid pool in diabetic rats may also influence<br>uptake. For example, the disappearance of rose bengal, a<br>bile acid-dependent cholephilic anion, from seru of the bile acid pool in diabetic rats may also influence<br>uptake. For example, the disappearance of rose bengal, a<br>bile acid-dependent cholephilic anion, from serum is in-<br>creased in diabetic rats, as is biliary excretion of the sine acid poor in that the rate indy this minimized pharmacologically or toxicologically active agents or de-<br>uptake. For example, the disappearance of rose bengal, a<br>bile acid-dependent cholephilic anion, from seru Preliminary studies of taurocholate transport into<br>hepatocytes isolated from normal, diabetic, and insulin-<br>normal process in home content when they cannot are treated diabetic rats indicate that the Km for uptake is generally quite small.<br>unchanged, whereas  $v_{max}$  is increased (Schwarz and of greater interest) excretion inhibited (Watkins and Noda, 1986). ger<br>
Preliminary studies of taurocholate transport into<br>
hepatocytes isolated from normal, diabetic, and insulin-<br>
treated diabetic rats indicate that the Km for uptake is<br>
un Preliminary studies of taurocholate transport into<br>hepatocytes isolated from normal, diabetic, and insulin-<br>treated diabetic rats indicate that the Km for uptake is<br>unchanged, whereas  $v_{max}$  is increased (Schwarz and<br>Watk BIOBILIARY FUNCTION<br>
V. Diabetes and Biotransformation<br>
Phase I Reactions<br>
Biotransformation is the process, primarily in the<br>
ver, by which the body either metabolizes chemicals to V. Diabetes and Biotransformation<br>A. Phase I Reactions<br>Biotransformation is the process, primarily in the<br>liver, by which the body either metabolizes chemicals to<br>pharmacologically or toxicologically active agents or de-A. Phase I Reactions<br>Biotransformation is the process, primarily in the<br>liver, by which the body either metabolizes chemicals to<br>pharmacologically or toxicologically active agents or de-<br>toxifies endogenous or exogenous co A. Thuse I Reuctions<br>Biotransformation is the process, primarily in the<br>liver, by which the body either metabolizes chemicals to<br>pharmacologically or toxicologically active agents or de-<br>toxifies endogenous or exogenous co Biotransformation is the process, primarily in the<br>liver, by which the body either metabolizes chemicals to<br>pharmacologically or toxicologically active agents or de-<br>toxifies endogenous or exogenous compounds and pre-<br>pare liver, by which the body either metabolizes chemicals to<br>pharmacologically or toxicologically active agents or de-<br>toxifies endogenous or exogenous compounds and pre-<br>pares them for elimination. One important component of<br> pharmacologically or toxicologically active agents or de-<br>toxifies endogenous or exogenous compounds and pre-<br>pares them for elimination. One important component of<br>biotransformation is the microsomal cytochrome P450-<br>depe toxifies endogenous or exogenous compounds and pre-<br>pares them for elimination. One important component of<br>biotransformation is the microsomal cytochrome P450-<br>dependent mono-oxidase system. The summary in table<br>1 suggests pares them for elimination. One important component obiotransformation is the microsomal cytochrome P450 dependent mono-oxidase system. The summary in table 1 suggests that there is no consistent evidence tha genetic or ch biotransformation is the microsomal cytochrome P450<br>dependent mono-oxidase system. The summary in table 1<br>suggests that there is no consistent evidence the<br>genetic or chemically-induced diabetes alters total cyto<br>chrome P4 1 suggests that there is no consistent evidence that genetic or chemically-induced diabetes alters total cyto-<br>chrome P450 concentrations in animal models. How-<br>ever, changes in heme content, when they occur, are<br>generally quite small.<br>Of greater interest is the observation ever, changes in heme content, when they occur, are

cyte plasma membrane vesicles indicates that there is<br>
no effect of diabetes on canalicular-enriched hepatocyte plasma membrane vesicles indicates that there is<br>
no effect of diabetes on canalicular taurocholate uptake<br>
i Watkins, unpublished results). More extensive work in<br>basolateral-enriched and canalicular-enriched hepato-<br>cyte plasma membrane vesicles indicates that there is<br>no effect of diabetes on canalicular taurocholate uptake<br>in basolateral-enriched and canalicular-enriched hepatocyte plasma membrane vesicles indicates that there is no effect of diabetes on canalicular taurocholate uptake into the presence or absence of ATP. In contrast, a two-fo cyte plasma membrane vesicles indicates that there is ously on effect of diabetes on canalicular taurocholate uptake (table 2 in the presence or absence of ATP. In contrast, a two-fold  $\frac{1}{20e}$  et increase in  $v_{max}$  is diabetic rats, whereas uptake into basolateral membranes is similar in preparations from normal and insularies in-<br>
lin-treated diabetic rats (Watkins et al., unpublished Tho<br>
results). These data indicate that the uncontr branes is similar in preparations from normal and insu-<br>lin-treated diabetic rats (Watkins et al., unpublished Thomas et al., 1989), fasting (Hong et al., 1987), and ace-<br>results). These data indicate that the uncontrolled results). These data indicate that the uncontrolled diabetic rat liver adapts to the increased bile acid pool by modulating the maximal velocity of taurocholate across at the basolateral surface of the hepatocyte and that Of greater interest is the observation that the locus of this diabetic effect is a particular isozyme of the P450 component of the mixed-function oxidase system, variously called cytochrome P450j, P450DM/j or P450IIE generally quite small.<br>
Of greater interest is the observation that the locus of<br>
this diabetic effect is a particular isozyme of the P450<br>
component of the mixed-function oxidase system, vari-<br>
ously called cytochrome P45 Of greater interest is the observation that the locus<br>this diabetic effect is a particular isozyme of the P4<br>component of the mixed-function oxidase system, va<br>ously called cytochrome P450j, P450DM/j or P450I<br>(table 2) (P this diabetic effect is a particular isozyme of the P450<br>component of the mixed-function oxidase system, vari-<br>ously called cytochrome P450j, P450DM/j or P450IIE<br>(table 2) (Past and Cook, 1982; Thomas et al., 1987; Yama-<br>z component of the mixed-function oxidase system, variously called cytochrome P450j, P450DM/j or P450IIE (table 2) (Past and Cook, 1982; Thomas et al., 1987; Yamazoe et al., 1989b). Although present in untreated normal rats, ously called cytochrome P450j, P450DM/j or P450IIE<br>(table 2) (Past and Cook, 1982; Thomas et al., 1987; Yama-<br>zoe et al., 1989b). Although present in untreated normal<br>rats, P450IIE is predominant in females (Waxman et al., zoe et al., 1989b). Although present in untreated normal rats, P450IIE is predominant in females (Waxman et al., 1989) and has been shown to be induced by treatment with zoe et al., 1989b). Although present in untreated normal<br>rats, P450IIE is predominant in females (Waxman et al.,<br>1989) and has been shown to be induced by treatment with<br>isoniazid (Ryan et al., 1985), dimethylsulfoxide and rats, P450IIE is predominant in females (Waxman et al., 1989) and has been shown to be induced by treatment with isoniazid (Ryan et al., 1985), dimethylsulfoxide and pyrazoles (Thomas et al., 1987), ethanol (Sato et al., 1 1989) and has been shown to be induced by treatment wit<br>isoniazid (Ryan et al., 1985), dimethylsulfoxide and pyrz<br>zoles (Thomas et al., 1987), ethanol (Sato et al., 198<br>Thomas et al., 1989), fasting (Hong et al., 1987), an reau and Schenkman, 1988a, b; Funae et al., 1988; Past zoles (Thomas et al., 1987), ethanol (Sato et al., 1981;<br>Thomas et al., 1989), fasting (Hong et al., 1987), and ace-<br>tone (Johansson et al., 1986), as well as by diabetes (Fav-<br>reau and Schenkman, 1988a, b; Funae et al., 1 Thomas et al., 1989), fasting (Hong et al., 1987), and acetone (Johansson et al., 1986), as well as by diabetes (Favreau and Schenkman, 1988a, b; Funae et al., 1988; Past and Cook, 1982), perhaps as a result of ketone bodi tone (Johansson et al., 1986), as well as by diabetes (Favreau and Schenkman, 1988a, b; Funae et al., 1988; Past and Cook, 1982), perhaps as a result of ketone bodies in the blood (Bellward et al., 1988; Favreau et al., 19 reau and Schenkman, 1988a, b; Funae et al., 1988; Past<br>and Cook, 1982), perhaps as a result of ketone bodies in the<br>blood (Bellward et al., 1988; Favreau et al., 1987) or in the<br>liver (Watkins et al., 1988). In fact, Song and Cook, 1982), perhaps as a result of ketone bodies in the blood (Bellward et al., 1988; Favreau et al., 1987) or in the liver (Watkins et al., 1988). In fact, Song and coworkers (1987) have measured an increase in P450I

*The effect of diabetes on total hepatic cytochrome P-450 levels*<br>Femalet **Reversel** Source TABLE 1<br>
. The effect of diabetes on total hepatic cytochrome P-450 levels<br>
Source Insulin Reversal<br>
SD\* rat STZ n.c. Dong et al., 1988; Faas and Carter, 1980<br>
SD rat STZ n.c. Eacho and Weiner, 1980 Animal Diabetes Malet Femalet Insulin Reversal<br>
SD<sup>\*</sup> rat STZ n.c. Dong et al., 1988; Faas and C.<br>
SD rat STZ n.c. Eacho and Weiner, 1980<br>
SD rat STZ 1 ves Eacho and Weiner, 1980; Favr Animal Diabetes Malet Femalet Reversal<br>
SD<sup>★</sup> rat STZ n.c. Dong et al., 1988; Faas and Carter, 1980<br>
SD rat STZ n.c. Eacho and Weiner, 1980; Favreau et al., 1987; Favreau and Schenkman<br>
SD rat STZ ↑ yes Eacho and Weiner, Dong et al., 1988; Faas and Carter, 1980<br>Eacho and Weiner, 1980<br>Eacho and Weiner, 1980; Favreau et al., 1987; Favreau and Schenkman,<br>1988a; Reinke et al., 1978<br>Faas and Carter, 1980; Reinke et al., 1978; Zysset and Tlach, SD<sup>\*</sup> rat STZ n.c. Dong et al., 1988; Faas and Carter, 1980<br>
SD rat STZ 1 yes Eacho and Weiner, 1980; Favreau et al., 1987; Favreau and Schenkman,<br>
SD rat STZ 1 yes Faas and Carter, 1980; Reinke et al., 1978; Zysset and Tl SD rat STZ n.c. Eacho and Weiner, 1980<br>
SD rat STZ † yes Eacho and Weiner, 1980; Favreau et al., 1987; Favreau<br>
SD rat STZ † yes Faas and Carter, 1980; Reinke et al., 1978; Zysset and<br>
SD rat STZ ↓ Taxes Mangels, 1988; Rei SD rat STZ ↑ yes Eacho and Weiner, 198<br>
SD rat STZ ↑ yes Faas and Carter, 1980<br>
SD rat STZ ↓ ↑ Watkins and Mangels,<br>
SD rat alloxan n.c. Dong et al., 1988<br>
Wistar rat alloxan ↑ Uchida et al., 1979 Note that the state of the <table>\n<tbody>\n<tr>\n<th>SD rat</th>\n<th>alloxan</th>\n<th>n.c.</th>\n<th>long et al., 1988</th>\n</tr>\n<tr>\n<td>Wistar rat</td>\n<td>alloxan</td>\n<td>↑</td>\n<td>Uchida et al., 1979</td>\n</tr>\n<tr>\n<td>Wistar rat</td>\n<td>alloxan</td>\n<td>n.c.</td>\n<td>Toda et al., 1987</td>\n</tr>\n<tr>\n<td>Wistar rat</td>\n<td>STZ</td>\n<td>n.c.</td>\n<td>Toda et al., 1987</td>\n</tr>\n<tr>\n<td>LE rat</td>\n<td>STZ</td>\n<td>n.c.</td>\n<td Wistar rat alloxan † Uchida et al., 1979<br>
Wistar rat alloxan n.c. Toda et al., 1987<br>
Wistar rat STZ n.c. Toda et al., 1987<br>
Holtzmann rat STZ n.c. Ackerman and Leibman, 1977<br>
BB/Wor rat genetic † yes Favreau and Schenkman, Wistar rat STZ n.c. Toda et al., 1987<br>
LE rat STZ n.c. Toda et al., 1987<br>
Holtzmann rat STZ n.c. Ackerman and Leibman, 1977<br>
BB/Wor rat genetic ↑ yes Favreau and Schenkman, 1988b<br>
WKY genetic 1 toda et al., 1988<br>
wKY gene BB/Wor rat genetic n.c. Dong et al., 1988<br>
WKY genetic ↓ Watkins and Mangels, 1987<br>
mice genetic ↑ ↑ Knodell et al., 1984; Rouer and L<br>
mice STZ ↑ ↑ yes Knodell et al., 1984; Rouer and L<br>
mice genetic n.c. Watkins and Klu \* VKY senetic ↓ Watkins and Mangels, 1987<br>
ince senetic ↑ ↑ Knodell et al., 1984; Rouer and Leroux, 1980<br>
senetic n.c. Watkins and Klueber, 1988<br>
\* SD, Sprague-Dawley; STZ, streptozotocin; LE, Long Evans, BB/Wor, Wistar,

TABLE 1

mice STZ<br>mice STZ<br>winners or mice (as indicated).<br> $\uparrow$  P450 levels:  $\uparrow$ , increased; the state of the sense<br>tice sense inc.<br>
the sense of the series of the series of the series of the series of P450 levels: ↑, increased; ↓ decreased; n.c., no change.

bile acid-dependent cholephilic anion, from seru<br>creased in diabetic rats, as is biliary excretion a<br>flow, whereas the serum disappearance of amar<br>bile acid-independent anion, is unchanged and ita<br>excretion inhibited (Watk

flow, whereas the serum disappearance of amaranth<br>bile acid-independent anion, is unchanged and its bili-<br>excretion inhibited (Watkins and Noda, 1986).<br>Preliminary studies of taurocholate transport in<br>the patocytes isolate

hepatocytes isolated from normal, diabetic, and insult<br>treated diabetic rats indicate that the Km for uptake<br>unchanged, whereas  $v_{max}$  is increased (Schwarz  $\varepsilon$ <br>Watkins, unpublished results). More extensive work<br>basolat

mo effect of diabetes on canalicular taurocholate uptake<br>in the presence or absence of ATP. In contrast, a two-fol<br>increase in  $v_{max}$  is observed in taurocholate uptake in<br>basolateral-enriched plasma membrane fractions fr in the presence or absence of ATP. In contrast, a two-fol<br>increase in  $v_{max}$  is observed in taurocholate uptake int<br>basolateral-enriched plasma membrane fractions fror<br>diabetic rats, whereas uptake into basolateral mem<br>br basolateral-enriched plasma membrane fractions from<br>diabetic rats, whereas uptake into basolateral mem-

basolateral-enriched plasma membrane fractions from<br>diabetic rats, whereas uptake into basolateral mem-<br>branes is similar in preparations from normal and insu-<br>lin-treated diabetic rats (Watkins et al., unpublished<br>results

results). These data indicate that the uncontrolled dia-

betic rat liver adapts to the increased bile acid pool by<br>modulating the maximal velocity of taurocholate across<br>the basolateral surface of the hepatocyte and that insu-<br>lin treatment normalizes this effect. Additional res lin treatment normalizes this effect. Additional research<br>is needed to unequivocally demonstrate that diabetes<br>does not alter canalicular membrane transport.

<sup>6</sup> WATKINS AND SANDERS **TABLE 2** *The effect ofdiabetes on hepatic cytochrome P-45011E levels*

Animal	<b>Diabetes</b> <b>STZ</b>	<b>Malet</b>	Insulin Reversal yes	<b>Source</b>		
$SD*$ rat				Bellward et al., 1988; Dong et al., 1988; Favreau et al., 1987; Favreau and Schenkman, 1988a; Yamazoe et al., 1989b		
SD rat	STZ.			Yamazoe et al., 1989a		
SD rat	alloxan		yes	Bellward et al., 1988; Dong et al., 1988; Past and Cook, 1982		
SD rat	alloxan			Yamazoe et al., 1989a		
LE rat	<b>STZ</b>		yes	Thomas et al., 1987		
<b>Fisher rat</b>	STZ/alloxan	n.c.		Chawalit et al., 1982		
<b>BB/Wor rat</b>	genetic		yes/no	Bellward et al., 1988; Dong et al., 1988; Favreau and Schenkman, 1988b		

 $\dagger$  P-450 levels:  $\dagger$ , increased;  $\downarrow$ , decreased; n.c., no change.<br>have come to varying conclusions concerning the effect of diabetes on total P450 content (table 1), many studies \* SD, Sprague Dawley; LE, Long Evans; BB/Wor, Fisher or Brattle  $\dagger$  P-450 levels:  $\uparrow$ , increased;  $\downarrow$ , decreased; n.c., no change.<br>have come to varying conclusions concerning the effect of diabetes on total P450 cont  $T$ P-450 levels:  $T$ , increased;  $J$ , decreased; n.c., no change.<br>have come to varying conclusions concerning the effectiable diabetes on total P450 content (table 1), many stude agree that cytochrome P450IIE is increased have come to varying conclusions concerning the effect of diabetes on total P450 content (table 1), many studies agree that cytochrome P450IIE is increased in streptozotocin-induced-, alloxan-induced-, or genetically-cause have come to varying concl<br>diabetes on total P450 co<br>agree that cytochrome P45<br>tocin-induced-, alloxan-indu<br>abetic animals (table 2).<br>Recent studies on the efabetes on total P450 content (table 1), many studies<br>ree that cytochrome P450IIE is increased in streptozo-<br>cin-induced-, alloxan-induced-, or genetically-caused di-<br>etic animals (table 2).<br>Recent studies on the effects of

tocin-induced-, alloxan-induced-, or genetically-caused diabetic animals (table 2).<br>Recent studies on the effects of diabetes on the P450-<br>mediated metabolism of various substrates are summa-<br>rized in table 3. This heterog right to the simulation of the sense<br>in the sense of diabetes on the P450-<br>neediated metabolism of various substrates are summa-<br>rized in table 3. This heterogeneous group of isozymes<br>has been shown in the rat to be modifi tramposed to the 2. The reflects of diabetes on the P450-<br>
Recent studies on the effects of diabetes on the P450-<br>
mediated metabolism of various substrates are summa-<br>
increased in table 3. This heterogeneous group of iso Recent studies on the effects of diabetes on the P450-<br>mediated metabolism of various substrates are summa-<br>rized in table 3. This heterogeneous group of isozymes<br>has been shown in the rat to be modified by diabetes in<br>a s mediated metabolism of various substrates are surized in table 3. This heterogeneous group of isoz<br>has been shown in the rat to be modified by diabet<br>a substrate-specific manner. The most studied read<br>are aniline hydroxyla rized in table 5. This heterogeneous group of isozymes<br>has been shown in the rat to be modified by diabetes in<br>a substrate-specific manner. The most studied reactions<br>are aniline hydroxylation and aminopyrine N-demethy-<br>la has been shown in the rat to be modified by diabetes in<br>a substrate-specific manner. The most studied reactions<br>are aniline hydroxylation and aminopyrine N-demethy-<br>lation, both of which seem to be dependent on the sex of<br> a substrate-specific manner. The most studied reactions nare aniline hydroxylation and aminopyrine N-demethy-<br>lation, both of which seem to be dependent on the sex of p<br>the animal (Faas and Carter, 1980; Rouer et al., 1982 are aniline hydroxylation and aminopyrine N-demethy<br>lation, both of which seem to be dependent on the sex of<br>the animal (Faas and Carter, 1980; Rouer et al., 1982<br>Skett and Joels, 1985). Induction of diabetes in male rat<br>b lation, both of which seem to be dependent on the sex of pyr<br>the animal (Faas and Carter, 1980; Rouer et al., 1982; dia<br>Skett and Joels, 1985). Induction of diabetes in male rats and<br>by alloxan, streptozotocin, or 6-aminon the animal (Faas and Carter, 1980; Rouer et al., 1982;<br>Skett and Joels, 1985). Induction of diabetes in male rats<br>by alloxan, streptozotocin, or 6-aminonicotinamide de-<br>creases activities of aminopyrine N-demethylase and<br>a Skett and Joels, 1985). Induction of diabetes in male rats<br>by alloxan, streptozotocin, or 6-aminonicotinamide de-<br>creases activities of aminopyrine N-demethylase and<br>aryl hydrocarbon [benzo(a)pyrene] hydroxylase—as well<br>as by alloxan, streptozotocin, or 6-aminonicotinamide decreases activities of aminopyrine N-demethylase and aryl hydrocarbon [benzo(a)pyrene] hydroxylase—as well as the biotransformation of hexobarbital—but increases aniline creases activities of aminopyrine N-demethylase are aryl hydrocarbon [benzo(a)pyrene] hydroxylase—as we as the biotransformation of hexobarbital—but increases aniline hydroxylase activity. In female rats, howeve induction aryl hydrocarbon [benzo(a)pyrene] hydroxylase—as well<br>as the biotransformation of hexobarbital—but increases<br>aniline hydroxylase activity. In female rats, however, ja<br>induction of diabetes increases the metabolism of aminas the biotransformation of hexobarbital—but increases<br>aniline hydroxylase activity. In female rats, however,<br>induction of diabetes increases the metabolism of amin-<br>opyrine, hexobarbital, aniline, and biphenyls. Insulin<br>r aniline hydroxylase activity. In female rats, however, induction of diabetes increases the metabolism of aminopyrine, hexobarbital, aniline, and biphenyls. Insulin reverses these changes in diabetic rats but has no effect induction of diabetes increases the metabolism of amin-<br>opyrine, hexobarbital, aniline, and biphenyls. Insulin<br>reverses these changes in diabetic rats but has no effect<br>on biotransformation in normal rats. Studies in mice, substrate-dependent effects. verses these changes in diabetic rats but has no effective in the individual polarization in normal rats. Studies in minimals, show simidstrate-dependent effects.<br>Building on these indications that hormonal interacy may p on biotransformation in normal rats. Studies in mice,<br>including genetically diabetic animals, show similar<br>substrate-dependent effects.<br>Building on these indications that hormonal interac-<br>tions may play a part in the effe

including genetically diabetic animals, show sim<br>substrate-dependent effects.<br>Building on these indications that hormonal inter<br>tions may play a part in the effects of diabetes, Yama<br>and coworkers (1989b) have demonstrated substrate-dependent effects.<br>Building on these indications that hormonal interations may play a part in the effects of diabetes, Yamaz<br>and coworkers (1989b) have demonstrated a relatio<br>ship between increased cytochrome P45 Building on these indications that hormonal interac-<br>tions may play a part in the effects of diabetes, Yamazoe<br>and coworkers (1989b) have demonstrated a relation-<br>ship between increased cytochrome P450IIE and deple-<br>tion o tions may play a part in the effects of diabetes, Yamazoe am<br>and coworkers (1989b) have demonstrated a relation-<br>ship between increased cytochrome P450IIE and deple-<br>tion of growth hormone, suggesting that this may be a cy and coworkers (1989b) have demonstrated a relation<br>ship between increased cytochrome P450IIE and deple<br>tion of growth hormone, suggesting that this may be<br>mechanism by which diabetes alters cytochrome P45<br>isozyme distribut ship between increased cytochrome P450IIE and depletion of growth hormone, suggesting that this may be a mechanism by which diabetes alters cytochrome P450 isozyme distribution. Another proposal states that insulin deficie tion of growth hormone, suggesting that this may be a<br>mechanism by which diabetes alters cytochrome P450<br>isozyme distribution. Another proposal states that insu-<br>lin deficiency, hyperlipidemia, hyperketonemia and dis-<br>turb mechanism by which diabetes alters cytochrome P450<br>isozyme distribution. Another proposal states that insu-<br>lin deficiency, hyperlipidemia, hyperketonemia and dis-<br>turbances in levels of circulating hormones together in-<br>d isozyme distribution. Another proposal states that insulin deficiency, hyperlipidemia, hyperketonemia and disturbances in levels of circulating hormones together induce changes in hepatic cytochrome P450 levels (Barnett et lin deficiency, hyperlipidemia, hyperketonemia and disturbances in levels of circulating hormones together induce changes in hepatic cytochrome P450 levels (Barnett et al., 1992). However, Kato and Yamazoe (1992) point out turbances in levels of circulating hormones together in-<br>duce changes in hepatic cytochrome P450 levels (Barnett<br>et al., 1992). However, Kato and Yamazoe (1992) point out<br>that, although the expression of sex-specific P450s duce changes in hepatic cytochrome P450 levels (Barnet et al., 1992). However, Kato and Yamazoe (1992) point ou that, although the expression of sex-specific P450s is regulated by growth hormone, thyroid hormone, sex hor m et al., 1992). However, Kato and Yamazoe (1992) point out inst<br>that, although the expression of sex-specific P450s is reg-<br>translated by growth hormone, thyroid hormone, sex hor-<br>mones, and other chemicals, there are no or that, although the expression of sex-specific P450s is regulated by growth hormone, thyroid hormone, sex hormones, and other chemicals, there are no or few cyto-<br>chrome P450s that show the sex-related differences in specie ulated by growth hormone, thyroid hormone, sex hor-<br>mones, and other chemicals, there are no or few cyto-<br>chrome P450s that show the sex-related differences in w<br>species other than rats and mice. Zysset and Tlach (1986)<br>Pa mones, and other chemicals, there are no or few cytocould speculate that xenobiotics activated by P450IIE chrome P450s that show the sex-related differences in would exert greater toxicity, and those inactivated by species

differences may account for apparent increases in metab-<br>olism in diabetic rats. Clearly, further research is needed<br>to substantiate or refute the role of growth hormone or oro rats as indicated.<br>differences may account for apparent increases in metab-<br>olism in diabetic rats. Clearly, further research is needed<br>to substantiate or refute the role of growth hormone or differences may account for apparent increases in metabolism in diabetic rats. Clearly, further research is needed to substantiate or refute the role of growth hormone or other growth factors in mediating changes in phase differences may account for apparent increases in metab-<br>olism in diabetic rats. Clearly, further research is needed<br>to substantiate or refute the role of growth hormone or<br>other growth factors in mediating changes in phas differences may account for apparent in<br>olism in diabetic rats. Clearly, further r<br>to substantiate or refute the role of gr<br>other growth factors in mediating change<br>transformational capacity of the liver.<br>Some apparent eff sm in diabetic rats. Clearly, further research is needed<br>substantiate or refute the role of growth hormone or<br>her growth factors in mediating changes in phase I bio-<br>ansformational capacity of the liver.<br>Some apparent effe

to substantiate or refute the role of growth hormone or other growth factors in mediating changes in phase I bio-<br>transformational capacity of the liver.<br>Some apparent effects of diabetes in humans, i.e.,<br>increased levels other growth factors in mediating changes in phase I bio-<br>transformational capacity of the liver.<br>Some apparent effects of diabetes in humans, i.e.,<br>increased levels of P450 and altered drug metabolizing<br>capacity, may be c transformational capacity of the liver.<br>Some apparent effects of diabetes in humans, i.e.<br>increased levels of P450 and altered drug metabolizing<br>capacity, may be confounded by the presence of live-<br>disease such as hepatiti Some apparent effects of diabetes in humans, i.e., increased levels of P450 and altered drug metabolizing capacity, may be confounded by the presence of liver disease such as hepatitis, cirrhosis, or fatty liver (Oltmanns increased levels of P450 and altered drug metabolizing capacity, may be confounded by the presence of live disease such as hepatitis, cirrhosis, or fatty liver (Olt manns et al., 1984; Salmela et al., 1980). Daintith and c capacity, may be confounded by the presence of liver disease such as hepatitis, cirrhosis, or fatty liver (Oltmanns et al., 1984; Salmela et al., 1980). Daintith and coworkers (1976) find that the plasma half-life of antidisease such as hepatitis, cirrhosis, or fatty liver (Oltmanns et al., 1984; Salmela et al., 1980). Daintith and coworkers (1976) find that the plasma half-life of anti-<br>pyrine is not different from control in diet-maintai manns et al., 1984; Salmela et al., 1980). Daintith and<br>coworkers (1976) find that the plasma half-life of anti-<br>pyrine is not different from control in diet-maintained<br>diabetic patients or those receiving tolbutamide, but coworkers (1976) find that the plasma half-life of anti-<br>pyrine is not different from control in diet-maintained<br>diabetic patients or those receiving tolbutamide, but<br>administration of insulin and chlorpropamide enhanced<br>d pyrine is not different from control in diet-maintained diabetic patients or those receiving tolbutamide, but administration of insulin and chlorpropamide enhanced drug clearance. Diabetics from whom insulin is withheld fo administration of insulin and chlorpropamide enhanced for 48 h excrete a larger portion of phenacetin as unmetabolized drug and a smaller amount as the O-deethylated conjugate than when their insulin is restored (Da-<br>jani et al., 1974). In the same study, metabolism of phenyl drug clearance. Diabetics from whom insulin is withheld<br>for 48 h excrete a larger portion of phenacetin as unme-<br>tabolized drug and a smaller amount as the O-deethyl-<br>ated conjugate than when their insulin is restored (Daated conjugate than when their insulin is restored (Da-<br>jani et al., 1974). In the same study, metabolism of<br>phenylbutazone and tolbutamide seems unchanged. Bio-<br>transformation of acetophenetidin is also decreased in tabolized drug and a smaller amount as the O-deethylated conjugate than when their insulin is restored (Dajani et al., 1974). In the same study, metabolism of phenylbutazone and tolbutamide seems unchanged. Bio-transformat ated conjugate than when their insulin is restored (Dajani et al., 1974). In the same study, metabolism of phenylbutazone and tolbutamide seems unchanged. Bio-<br>transformation of acetophenetidin is also decreased in<br>alloxan iani et al., 1974). In the same study, metabolism of<br>phenylbutazone and tolbutamide seems unchanged. Bio-<br>transformation of acetophenetidin is also decreased in<br>alloxan-induced diabetic rabbits (Dajani and Kayyali,<br>1973). phenylbutazone and tolbutamide seems unchanged. Bio-<br>transformation of acetophenetidin is also decreased in<br>alloxan-induced diabetic rabbits (Dajani and Kayyali,<br>1973). Although Redman and Prescott (1973) report no<br>inducti transformation of acetophenetidin is also decreased<br>alloxan-induced diabetic rabbits (Dajani and Kayy,<br>1973). Although Redman and Prescott (1973) report<br>induction of microsomal enzymes by tolbutamide in<br>abetics, there is s alloxan-induced diabetic rabbits (Dajani and Kayyali, 1973). Although Redman and Prescott (1973) report no<br>induction of microsomal enzymes by tolbutamide in di-<br>abetics, there is some evidence of wide, perhaps geneti-<br>cal induction of microsomal enzymes by tolbutamide in diabetics, there is some evidence of wide, perhaps genetically controlled variation in tolbutamide metabolism among diabetic patients (Melander et al., 1978; Scott and Poff induction of microsomal enzymes by tolbuta<br>abetics, there is some evidence of wide, perh<br>cally controlled variation in tolbutamide r<br>among diabetic patients (Melander et al., 1<br>and Poffenbarger, 1979; Ueda et al., 1963).<br>I abetics, there is some evidence of wide, perhaps gened-<br>cally controlled variation in tolbutamide metabolism<br>among diabetic patients (Melander et al., 1978; Scott<br>and Poffenbarger, 1979; Ueda et al., 1963).<br>In summary, the

among diabetic patients (Melander et al., 1978; Scott<br>and Poffenbarger, 1979; Ueda et al., 1963).<br>In summary, the numerous alterations in microsomal<br>cytochrome P450-mediated reactions in diabetic hu-<br>mans and laboratory an and Poffenbarger, 1979; Ueda et al., 1963).<br>In summary, the numerous alterations in microsomal<br>cytochrome P450-mediated reactions in diabetic hu-<br>mans and laboratory animals vary widely, depending on<br>studied substrate, iso cytochrome P450-mediated reactions in diabetic humans and laboratory animals vary widely, depending on studied substrate, isozyme, sex, species, and severity of disease. Although the data indicate preferential expression o cytochrome P450-mediated reactions in diabetic humans and laboratory animals vary widely, depending on studied substrate, isozyme, sex, species, and severity of disease. Although the data indicate preferential expression o mans and laboratory animals vary widely, depending on<br>studied substrate, isozyme, sex, species, and severity of<br>disease. Although the data indicate preferential expres-<br>sion of cytochrome P450IIE in diabetic animals, more<br> studied substrate, isozyme, sex, species, and severity of<br>disease. Although the data indicate preferential expres-<br>sion of cytochrome P450IIE in diabetic animals, more<br>specific studies of the effects of insulin-dependent a disease. Although the data indicate preferential expression of cytochrome P450IIE in diabetic animals, more specific studies of the effects of insulin-dependent and insulin-independent diabetes mellitus on hepatic biotrans specific studies of the effects of insulin-dependent and<br>insulin-independent diabetes mellitus on hepatic bio-<br>transformation in humans are needed. If cytochrome<br>P450IIE is increased consistently in humans, then one<br>could specific studies of the effects of insulin-dependent and<br>insulin-independent diabetes mellitus on hepatic bio-<br>transformation in humans are needed. If cytochrome<br>P45OIIE is increased consistently in humans, then one<br>could insulin-independent diabetes mellitus on hepatic bio-<br>transformation in humans are needed. If cytochrome<br>P450IIE is increased consistently in humans, then one<br>could speculate that xenobiotics activated by P450IIE<br>would exe transformation in numans are needed. If cytochrome<br>P450IIE is increased consistently in humans, then one<br>could speculate that xenobiotics activated by P450IIE<br>would exert greater toxicity, and those inactivated by<br>P450IIE P45011E Is increased consistently in numans, then one could speculate that xenobiotics activated by P450IIE would be ineffective: a higher dose would be required to acheive therapeutic efficacy. Future efforts need to addr

PHARMACOLOGICAL REVIEWS

# *B. Phase II Conjugations*

DIABETES MELLITUS AND HEPATOBILIARY FUNCTION<br>Biotransformation also involves the enzymatically abetic liver (McLennan<br>mediated conjugation of a xenobiotic with an endoge-<br>nous water-soluble moiety such as sulfate, glutathi DIABETES MELLITUS A<br>B. Phase II Conjugations<br>Biotransformation also involves the enzymatica<br>mediated conjugation of a xenobiotic with an endog<br>nous water-soluble moiety such as sulfate, glutathion B. Phase II Conjugations<br>Biotransformation also involves the enzymaticall<br>mediated conjugation of a xenobiotic with an endoge<br>nous water-soluble moiety such as sulfate, glutathion<br>or glucuronate. The resulting conjugate is  $\mu$ . Frace II Conjugations<br>
Biotransformation also involves the enzymatically<br>
mediated conjugation of a xenobiotic with an endoge-<br>
nous water-soluble moiety such as sulfate, glutathione,<br>
or glucuronate. The resulting Biotransformation also involves the enz<br>mediated conjugation of a xenobiotic with a<br>nous water-soluble moiety such as sulfate, g<br>or glucuronate. The resulting conjugate<br>readily excreted in the urine, bile, or feces.<br>Glucur ediated conjugation of a xenobiotic with an endogenus water-soluble moiety such as sulfate, glutathion glucuronate. The resulting conjugate is usuall adily excreted in the urine, bile, or feces.<br>Glucuronidation is the most

nous water-soluble moiety such as sulfate, glutathione,<br>or glucuronate. The resulting conjugate is usually<br>readily excreted in the urine, bile, or feces.<br>Glucuronidation is the most-studied phase II path-<br>way, and table 4 or glucuronate. The resulting conjugate is usua<br>readily excreted in the urine, bile, or feces.<br>Glucuronidation is the most-studied phase II pa<br>way, and table 4 indicates that many of the observe<br>ffects are substrate-specif readily excreted in the urine, bile, or feces.<br>Glucuronidation is the most-studied phase II path-<br>way, and table 4 indicates that many of the observed<br>effects are substrate-specific, sex-related, and species-<br>dependent. Di Glucuronidation is the most-studied phase II pathway, and table 4 indicates that many of the observed effects are substrate-specific, sex-related, and species-<br>dependent. Diabetes inhibits conjugation of testosterone (Schr way, and table 4 indicates that many of the observ<br>effects are substrate-specific, sex-related, and specid<br>dependent. Diabetes inhibits conjugation of testostero<br>(Schriefers et al., 1966; Watkins and Klueber, 198<br>Watkins a effects are substrate-specific, sex-related, and species-<br>dependent. Diabetes inhibits conjugation of testosterone<br>(Schriefers et al., 1966; Watkins and Klueber, 1988;<br>Watkins and Mangels, 1987; Watkins and Klueber, 1988;<br> dependent. Diabetes inhibits conjugation of testostero (Schriefers et al., 1966; Watkins and Klueber, 1983), 1-napthol (Grant and Duthie, 1987; Watkins and Klueber, 1983), phenolection and Mangels, 1987; Watkins and Kluebe (Schriefers et al., 1966; Watkins and Klueber, 19<br>Watkins and Mangels, 1987; Watkins et al., 1988), 1-na;<br>thol (Grant and Duthie, 1987; Watkins and Klueber, 19<br>Watkins and Mangels, 1987; Watkins et al., 1988), pher<br>phthale thol (Grant and Duthie, 1987; Watkins and Klueber, 1988; Watkins and Mangels, 1987; Watkins et al., 1988), phenol-<br>phthalein (Grant and Duthie, 1987), salicylic acid (Emudi-<br>anughe et al., 1988), and 1-aminophenol (Mullerthol (Grant and Duthie, 1987; Watkins and Klueber, 1988;<br>Watkins and Mangels, 1987; Watkins et al., 1988), phenol-<br>phthalein (Grant and Duthie, 1987), salicylic acid (Emudi-<br>anughe et al., 1988), and 1-aminophenol (Muller Watkins and Mangels, 1987; Watkins et al., 1988), phenolphthale<br>in (Grant and Duthie, 1987), salicylic acid (Emudianughe et al., 1988), and 1-aminophenol (Muller-Oerling-<br>hausen et al., 1967) but enhances glucuronidation phthalein (Grant and Duthie, 1987), salicylic acid (Emudianughe et al., 1988), and 1-aminophenol (Muller-Oerling-<br>hausen et al., 1967) but enhances glucuronidation of<br>acetaminophen (Price and Jollow, 1982). Conjugation of<br> anughe et al., 1988), and 1-aminophenol (Muller-Oerlin hausen et al., 1967) but enhances glucuronidation acetaminophen (Price and Jollow, 1982). Conjugation 4-nitrophenol, studied in rats (Carnovale et al., 198<br>Hawksworth hausen et al., 1967) but enhances glucuronidation of acetaminophen (Price and Jollow, 1982). Conjugation of 4-nitrophenol, studied in rats (Carnovale et al., 1992; Hawksworth and Morrison, 1980; Morrison and Hawksworth 198 acetaminophen (Price and Jollow, 1982). Conjugation of<br>4-nitrophenol, studied in rats (Carnovale et al., 1992;<br>Hawksworth and Morrison, 1980; Morrison and Hawk-<br>sworth 1982, 1984), mice (Rouer et al., 1981), rabbits (Hi-<br> 4-nitrophenol, studied in rats (Carnovale et al., 1992; Hawksworth and Morrison, 1980; Morrison and Hawksworth 1982, 1984), mice (Rouer et al., 1981), rabbits (Hinohara et al., 1974), and isolated rat hepatocytes (Eacho an Hawksworth and Morrison, 1980; Morrison and Haw.<br>sworth 1982, 1984), mice (Rouer et al., 1981), rabbits (H<br>nohara et al., 1974), and isolated rat hepatocytes (Each<br>and Weiner, 1980; Eacho et al., 1981a,b) seems to be u<br>aff sworth 1982, 1984), mice (Rouer et al., 1981), rabbits<br>nohara et al., 1974), and isolated rat hepatocytes (E<br>and Weiner, 1980; Eacho et al., 1981a,b) seems to be<br>affected in female diabetics, but either enhanced or in<br>ited nohara et al., 1974), and isolated rat hepatocytes (Eacho and Weiner, 1980; Eacho et al., 1981a,b) seems to be unaffected in female diabetics, but either enhanced or inhibited in males, depending on species. Estrone glucur and Weiner, 1980; Eacho et al., 1981a,b) seems to be unaffected in female diabetics, but either enhanced or inhibited in males, depending on species. Estrone glucuronidation is not affected by diabetes (Watkins and Mangel affected in female diabetics, but either enhanced or inhibited in males, depending on species. Estrone glucuronidation is not affected by diabetes (Watkins and Mangels, 1987; Watkins et al., 1988), whereas conflicting effe ited in males, depending on species. Estrone glucuronidation is not affected by diabetes (Watkins and Mangels, 1987; Watkins et al., 1988), whereas conflicting effects on the conjugation of bilirubin are seen (Rouer et al. tion is not affected by diabetes (Watkins and Mangels, 1987; Watkins et al., 1988), whereas conflicting effects on the conjugation of bilirubin are seen (Rouer et al., 1981, 1982; Tunon et al., 1991; Gonzalez and Fevery, 1 1987; Watkins et al., 1988), whereas conflicting effects on<br>the conjugation of bilirubin are seen (Rouer et al., 1981<br>1982; Tunon et al., 1991; Gonzalez and Fevery, 1992)<br>Morrison and Hawksworth (1982) suggest that variati the conjugation of bilirubin are seen (Rouer et al., 1981, 1982; Tunon et al., 1991; Gonzalez and Fevery, 1992).<br>Morrison and Hawksworth (1982) suggest that variations in glucuronidation of substrates in streptozotocin-tre 1982; Tunon et al., 1991; Gonzalez and Fevery, 1992)<br>Morrison and Hawksworth (1982) suggest that variations<br>in glucuronidation of substrates in streptozotocin-treated<br>male rats may be owing to an alteration of the membrane Morrison and Hawksworth (1982) suggest that variations<br>in glucuronidation of substrates in streptozotocin-treated<br>male rats may be owing to an alteration of the membrane<br>lipid environment, rather than a transferase modific in glucuronidation of substrates in streptozotocin-treated<br>
male rats may be owing to an alteration of the membrane<br>
lipid environment, rather than a transferase modification,<br>
that might be caused by either streptozotoci male rats may be owing to an alteration of the membrane  $\frac{1}{10}$ <br>lipid environment, rather than a transferase modification, direct may that might be caused by either streptozotocin or diabetes. The<br>Mottino et al. (1991) lipid environment, rather than a transferase mod<br>that might be caused by either streptozotocin or of<br>Mottino et al. (1991) also postulate that lipid differ<br>the microenvironment level may explain variation<br>organs in UDP-glu at might be caused by either streptozotocin or diabetes.<br>
ottino et al. (1991) also postulate that lipid differences at<br>
e microenvironment level may explain variations among<br>
gans in UDP-glucuronosyltransferase activity.<br>

Mottino et al. (1991) also postulate that lipid differences<br>the microenvironment level may explain variations amon<br>organs in UDP-glucuronosyltransferase activity.<br>Diabetes has diverse effects on the glutathione<br>transferase the microenvironment level may explain variations am<br>organs in UDP-glucuronosyltransferase activity.<br>Diabetes has diverse effects on the glutathione<br>transferases as shown in table 5. The activity of glu<br>thione S-transferas organs in UDP-glucuronosyltransferase activity.<br>
Diabetes has diverse effects on the glutathione S-<br>
transferases as shown in table 5. The activity of gluta-<br>
thione S-transferase toward 1-chloro-2,4-dinitrobenzene<br>
is dec Diabetes has diverse effects on the glutathione S-<br>transferases as shown in table 5. The activity of gluta-<br>thione S-transferase toward 1-chloro-2,4-dinitrobenzene<br>is decreased in streptozotocin- and alloxan-induced dia-<br>b transferases as shown in table 5. The activity of gluta-<br>thione S-transferase toward 1-chloro-2,4-dinitrobenzene<br>is decreased in streptozotocin- and alloxan-induced dia-<br>betic rats (Aniya et al., 1989; Muller-Oerlinghausen is decreased in streptozotocin- and alloxan-induced diabetic rats (Aniya et al., 1989; Muller-Oerlinghausen et al., 1967; Thomas et al., 1989; Watkins and Mangels, 1987; Watkins et al., 1988). In contrast, transferase acti is decreased in streptozotocin- and alloxan-induced dia-<br>betic rats (Aniya et al., 1989; Muller-Oerlinghausen et<br>al., 1967; Thomas et al., 1989; Watkins and Mangels,<br>1987; Watkins et al., 1988). In contrast, transferase ou betic rats (Aniya et al., 1989; Muller-Oerlinghausen et col., 1967; Thomas et al., 1989; Watkins and Mangels, les<br>1987; Watkins et al., 1988). In contrast, transferase ou<br>activity is increased in streptozotocin-induced mic al., 1967; Thomas et al., 1989; Watkins and Mangels, 1987; Watkins et al., 1988). In contrast, transferase activity is increased in streptozotocin-induced mice (Agius and Gidari, 1985; Rouer et al., 1981, 1982) but is unch 1987; Watkins et al., 1988). In contrast, transferase activity is increased in streptozotocin-induced mice (Agius and Gidari, 1985; Rouer et al., 1981, 1982) but is unchanged in genetically diabetic mice (Rouer et al., 198 activity is increased in streptozotocin-induced mice conditions (Agius and Gidari, 1985; Rouer et al., 1981, 1982) but is acid unchanged in genetically diabetic mice (Rouer et al., solume) 1981, 1982) and rats (Watkins and (Agius and Gidari, 1985; Rouer et al., 1981, 1982) but is unchanged in genetically diabetic mice (Rouer et al., 1981, 1982) and rats (Watkins and Mangels, 1987). Diabetes decreases the conjugation of ethacrynic acid with unchanged in genetically diabetic mice (Rouer et al., solution)<br>1981, 1982) and rats (Watkins and Mangels, 1987). Diabletes decreases the conjugation of ethacrynic acid with videnduathione in streptozotocin-induced rats (W 1981, 1982) and rats (Watkins and Mangels, 1987). Diabetes decreases the conjugation of ethacrynic acid with glutathione in streptozotocin-induced rats (Watkins et al., 1988) and in genetically diabetic rats (Watkins and M abetes decreases the conjugation of ethacrynic acid with<br>
yiding bile acids and phospholipids to the duodenum, (b)<br>
glutathione in streptozotocin-induced rats (Watkins et partially neutralizes acidic chyme from the stomach glutathione in streptozotocin-induced rats (Watkins et al., 1988) and in genetically diabetic rats (Watkins and Mangels, 1987) and mice (Watkins and Klueber, 1988). Conjugation of sulfobromophthalein is decreased in strept al., 1988) and in genetically diabetic rats (Watkins and Mangels, 1987) and mice (Watkins and Klueber, 1988).<br>Conjugation of sulfobromophthalein is decreased in streptozotocin-induced rats (Watkins et al., 1988) but not i Mangels, 1987) and mice (Watkins and Klueber, 19<br>Conjugation of sulfobromophthalein is decreased<br>streptozotocin-induced rats (Watkins et al., 1988)<br>not in genetically diabetic rats (Watkins and Mang<br>1987) or mice (Watkins

EPATOBILIARY FUNCTION<br>transpeptidase activity is dramatically increased in di-<br>abetic liver (McLennan et al., 1991; Watkins and Smith, EPATOBILIARY FUNCTION<br>transpeptidase activity is dramatically increased in di-<br>abetic liver (McLennan et al., 1991; Watkins and Smith,<br>1993), perhaps as an attempt to conserve glutathione by EPATOBILIARY FUNCTION 7<br>
1993), perhaps as an attempt to conserve glutathione by<br>
activation of the hepatic  $\gamma$ glutamyl cycle. transpeptidase activity is dramatically increabetic liver (McLennan et al., 1991; Watkins 1993), perhaps as an attempt to conserve glue activation of the hepatic  $\gamma$ -glutamyl cycle.<br>Other conjugation reactions are also i anspeptidase activity is dramatically increased in di-<br>etic liver (McLennan et al., 1991; Watkins and Smith,<br>93), perhaps as an attempt to conserve glutathione by<br>tivation of the hepatic  $\gamma$ -glutamyl cycle.<br>Other conjuga

abetic liver (McLennan et al., 1991; Watkins and Smith, 1993), perhaps as an attempt to conserve glutathione by activation of the hepatic  $\gamma$ -glutamyl cycle.<br>Other conjugation reactions are also influenced by diabetes. S 1993), perhaps as an attempt to conserve glutathione by<br>activation of the hepatic  $\gamma$ -glutamyl cycle.<br>Other conjugation reactions are also influenced by<br>diabetes. Sulfation of bile acids (Kirkpatrick and Kraft,<br>1984), ac activation of the hepatic  $\gamma$ -glutamyl cycle.<br>
Other conjugation reactions are also influenced by<br>
diabetes. Sulfation of bile acids (Kirkpatrick and Kraft,<br>
1984), acetaminophen (Price and Jollow, 1982), cortisol,<br>
and Other conjugation reactions are also influenced by<br>diabetes. Sulfation of bile acids (Kirkpatrick and Kraft,<br>1984), acetaminophen (Price and Jollow, 1982), cortisol,<br>and dehydroepiandrosterone (Singer et al., 1981) is en-<br> 1984), acetaminophen (Price and Jollow, 1982), cortisol, and dehydroepiandrosterone (Singer et al., 1981) is enhanced in diabetic rodents. Diabetes causes significant alterations in estrogen metabolism (DeHertogh et al., 1 1981), which affects many biotransformation reactions. and dehydroepiandrosterone (Singer et al., 1981) is enhanced in diabetic rodents. Diabetes causes significant<br>alterations in estrogen metabolism (DeHertogh et al.,<br>1981), which affects many biotransformation reactions.<br>Fin hanced in diabetic rodents. Diabetes causes significal<br>terations in estrogen metabolism (DeHertogh et<br>1981), which affects many biotransformation reactio<br>Finally, Toda and coworkers (1987) have observed<br>decrease in N-acety alterations in estrogen metabolism (DeHertogh et al., 1981), which affects many biotransformation reactions. Finally, Toda and coworkers (1987) have observed a decrease in N-acetyltransferase activity in both strepto-zotoc 1981), which affects many biotransformation reactions.<br>Finally, Toda and coworkers (1987) have observed a<br>decrease in N-acetyltransferase activity in both strepto-<br>zotocin- and alloxan-treated male rats. In contrast, sev-<br> Finally, Toda and coworkers (1987) have observed a decrease in N-acetyltransferase activity in both strepto-<br>zotocin- and alloxan-treated male rats. In contrast, several studies have been reviewed that indicate the rapid<br>a decrease in N-acetyltransferase activity in both strepto-<br>zotocin- and alloxan-treated male rats. In contrast, sev-<br>eral studies have been reviewed that indicate the rapid<br>acetylator phenotype is more prevalent among both zotocin- and alloxan-treated male rats. In contrast, several studies have been reviewed that indicate the rapid<br>acetylator phenotype is more prevalent among both type<br>I and type II diabetics (Evans, 1992). Apparently, the<br> eral studies have been reviewed that indicate the rapid<br>acetylator phenotype is more prevalent among both type<br>I and type II diabetics (Evans, 1992). Apparently, the<br>rapid phenotype is twice as likely to be associated with acetylator phenotype is more prevalent among both ty<br>I and type II diabetics (Evans, 1992). Apparently, t<br>rapid phenotype is twice as likely to be associated wi<br>insulin-dependent diabetes, but the correlation wi<br>non-insuli I and type II diabetics (Evans, 1992). Apparently, the rapid phenotype is twice as likely to be associated with insulin-dependent diabetes, but the correlation with non-insulin-dependent diabetes is not as strong. Unfortun rapid phenotype is twice as likely to be associated v<br>insulin-dependent diabetes, but the correlation v<br>non-insulin-dependent diabetes is not as strong. Un<br>tunately, the molecular mechanism for this appar<br>difference in ace sulin-dependent diabetes, but the correlation with<br>n-insulin-dependent diabetes is not as strong. Unfor-<br>nately, the molecular mechanism for this apparent<br>fference in acetylation has not yet been examined.<br>Efforts to pinpo

non-insulin-dependent diabetes is not as strong. Unfor-<br>tunately, the molecular mechanism for this apparent<br>difference in acetylation has not yet been examined.<br>Efforts to pinpoint the mechanism of these diabetic<br>effects o tunately, the molecular mechanism for this apparem<br>difference in acetylation has not yet been examined.<br>Efforts to pinpoint the mechanism of these diabetive<br>ffects on phase II biotransformation reactions have<br>shown that in difference in acetylation has not yet been examined.<br>Efforts to pinpoint the mechanism of these diabetic<br>effects on phase II biotransformation reactions have<br>shown that in vivo levels of uridine diphosphoglucuronic<br>acid (H Efforts to pinpoint the mechanism of these diabetic<br>effects on phase II biotransformation reactions have<br>shown that in vivo levels of uridine diphosphoglucuronic<br>acid (Hinohara et al., 1974; Schriefers et al., 1966) and<br>gl effects on phase II biotransformation reactions have<br>shown that in vivo levels of uridine diphosphoglucuronic<br>acid (Hinohara et al., 1974; Schriefers et al., 1966) and<br>glutathione (Younes et al., 1980), and in vitro activi shown that in vivo levels of uridine diphosphoglucuronic<br>acid (Hinohara et al., 1974; Schriefers et al., 1966) and<br>glutathione (Younes et al., 1980), and in vitro activity of<br>UDP-glucose dehydrogenase (Hinohara et al., 197 acid (Hinohara et al., 1974; Schriefers et al., 1966) and glutathione (Younes et al., 1980), and in vitro activity UDP-glucose dehydrogenase (Hinohara et al., 197<br>Muller-Oerlinghausen et al., 1967) are all depressed invers glutathione (Younes et al., 1980), and in vitro activity of UDP-glucose dehydrogenase (Hinohara et al., 1974 Muller-Oerlinghausen et al., 1967) are all depressed in livers of diabetic animals, whereas the activities of UDP UDP-glucose dehydrogenase (Hinohara et al., 197<br>Muller-Oerlinghausen et al., 1967) are all depressed<br>livers of diabetic animals, whereas the activities of UE<br>glucuronic acid pyrophosphatase and D-glucuronic ac<br>1-phosphatas Muller-Oerlinghausen et al., 1967) are all depressed in<br>livers of diabetic animals, whereas the activities of UDP-<br>glucuronic acid pyrophosphatase and D-glucuronic acid-<br>1-phosphatase (Hinohara et al., 1974) and the concen livers of diabetic animals, whereas the activities of UDP-<br>glucuronic acid pyrophosphatase and D-glucuronic acid-<br>1-phosphatase (Hinohara et al., 1974) and the concen-<br>tration of the oxidized form of nicotinamide adenine<br>d glucuronic acid pyrophosphatase and D-glucuronic acid-<br>1-phosphatase (Hinohara et al., 1974) and the concentration of the oxidized form of nicotinamide adenine<br>dinucleotide (Badawy and Evans, 1977) are enhanced.<br>These chan 1-phosphatase (Hinohara et al., 1974) and the tration of the oxidized form of nicotinamid dinucleotide (Badawy and Evans, 1977) are These changes in the conjugation pathway begin to explain the diverse effects observed. These changes in the conjugation pathway may only<br>begin to explain the diverse effects observed.<br>VI. Diabetes-induced Changes in Bile Production<br>A General Considerations Regarding Bile Formation *A. General Considerations Regarding Bile Formation***<br>** *A. General Considerations Regarding Bile Formation***<br>
A. General Considerations Regarding Bile Formation<br>
Bile. the exocrine secretion of the liver. provides a** 

A. General Considerations Regarding Bile Formation<br>Bile, the exocrine secretion of the liver, provides a<br>route of excretion for such endogenous and exogenous VI. Diabetes-induced Changes in Bile Production<br>A. General Considerations Regarding Bile Formation<br>Bile, the exocrine secretion of the liver, provides a<br>route of excretion for such endogenous and exogenous<br>compounds as bil A. General Considerations Regarding Bile Formation<br>Bile, the exocrine secretion of the liver, provides a<br>route of excretion for such endogenous and exogenous<br>compounds as bile acids, bilirubin, phospholipids, cho-<br>lesterol A. General Considerations negaraing Bile Formation<br>Bile, the exocrine secretion of the liver, provides<br>route of excretion for such endogenous and exogenou<br>compounds as bile acids, bilirubin, phospholipids, ch<br>lesterol, wat Bile, the exocrine secretion of the liver, provides a route of excretion for such endogenous and exogenous compounds as bile acids, bilirubin, phospholipids, cholesterol, water- and lipid-soluble drugs and toxins. Aque-<br>ou route of excretion for such endogenous and exogenous<br>compounds as bile acids, bilirubin, phospholipids, cho-<br>lesterol, water- and lipid-soluble drugs and toxins. Aque-<br>ous bile is suitable for the excretion of water-solubl compounds as bile acids, bilirubin, phospholipids, cho-<br>lesterol, water- and lipid-soluble drugs and toxins. Aque-<br>ous bile is suitable for the excretion of water-soluble<br>compounds and their metabolites. Micelle forming bi lesterol, water- and lipid-soluble drugs and toxins. Aque-<br>ous bile is suitable for the excretion of water-soluble<br>compounds and their metabolites. Micelle forming bile<br>acids above their critical micellar concentration al ous bile is suitable for the excretion of water-soluble<br>compounds and their metabolites. Micelle forming bile<br>acids above their critical micellar concentration allow<br>solubilization of lipid-soluble compounds in bile. Bile<br> compounds and their metabolites. Micelle forming bile<br>acids above their critical micellar concentration allow<br>solubilization of lipid-soluble compounds in bile. Bile<br>also (*a*) assists in fat digestion and absorption by pr acids above their critical micellar concentration allow<br>solubilization of lipid-soluble compounds in bile. Bile<br>also  $(a)$  assists in fat digestion and absorption by pro-<br>viding bile acids and phospholipids to the duodenum solubilization of lipid-soluble compounds in bile. B<br>also (*a*) assists in fat digestion and absorption by p<br>viding bile acids and phospholipids to the duodenum,<br>partially neutralizes acidic chyme from the stoma<br>and (*c*) also  $(a)$  assists in fat digestividing bile acids and phosphopartially neutralizes acidic  $\alpha$  and  $(c)$  plays an immunologic noglobulin A to the intestine. Osmosis is considered to b ding bile acids and phospholipids to the duodenum,  $(b)$ <br>rtially neutralizes acidic chyme from the stomach,<br> $d(c)$  plays an immunological role by delivering immu-<br>globulin A to the intestine.<br>Osmosis is considered to be the

partially neutralizes acidic chyme from the stomad and (c) plays an immunological role by delivering imm<br>noglobulin A to the intestine.<br>Osmosis is considered to be the major mechanism<br>water movement during bile formation, and  $(c)$  plays an immunological role by delivering imm<br>noglobulin A to the intestine.<br>Osmosis is considered to be the major mechanism<br>water movement during bile formation, although hyd<br>static pressure may affect bile form moglobulin A to the intestine.<br>
Osmosis is considered to be the major mechanism of<br>
water movement during bile formation, although hydro-<br>
static pressure may affect bile formation under experi-<br>
mental and pathological co

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# PHARMACOLOGICAL REVIEWS



**Cl) ., ABLE 3**<br>5 unless oth<br>cated to inc **Cl)**





\*, insulin reverses effects; **\***, insulin has no effect

DIABETES MELLITIJS AND HEPATOBILIARY FUNCTION <sup>9</sup> EURE DIABETES MELLITUS AND HEPATOBILIARY FUNCTION<br>ent is provided by organic and inorganic solutes secreted<br>into bile. The interrelationships among different trans-DIABETES MELLITUS AND HEPATOBILIARY FUNCTION<br>
ent is provided by organic and inorganic solutes secreted<br>
into bile. The interrelationships among different trans-<br>
port processes, metabolic events, and bile formation are DIABETES MELLITUS AND HEPATOBILIARY FUNCTION<br>
ent is provided by organic and inorganic solutes secreted<br>
into bile. The interrelationships among different trans-<br>
port processes, metabolic events, and bile formation are<br>
i port processes, metabolic events, and bile formation are<br>incompletely understood. Details of earlier studies can<br>be found in several comprehensive reviews (Anwer, ent is provided by organic and inorganic solutes secreted<br>into bile. The interrelationships among different trans-<br>port processes, metabolic events, and bile formation are<br>incompletely understood. Details of earlier studie into bile. The interrelationships among different transport processes, metabolic events, and bile formation are<br>
and the completely understood. Details of earlier studies can<br>
ab found in several comprehensive reviews (Anw **Fract Processes, metabolic events, and bile formation are<br>
<b>i** when the most processes, metabolic events, and bile formation are<br>
and the found in several comprehensive reviews (Anwer,<br>
1991; Arias et al., 1993; Erlinger, **be found in several comprehensive reviews (Anwer, 1991; Arias et al., 1993; Erlinger, 1988; Klaassen and Watkins, 1984; Moseley and Boyer, 1985; Suchy, 1989).<br>
<b>...** secreted into the canalicular space that is surrounded

 $\frac{36}{25}$ <br>  $\frac{36}{25}$ <br> Solution of tight junctions also serves as morphological<br>
Solution of tight junctions also serves as morphological<br>
Solution of tight junctions also serves as morphological<br>
Solution of tight junctions also serves as morph **Figure 1.1 ...**  $\begin{array}{c}\n\overline{1} & \overline{1} & \overline{1} \\
\overline{2} & \overline{2} & \overline{2} \\
\overline{3} & \overline{4} & \overline{2} \\
\overline{4} & \overline{4} & \overline{2} \\
\overline{5} & \overline{6} & \overline{2} \\
\overline{6} & \overline{6} & \overline{6} \\
\overline{7} & \overline{8} & \overline{2} \\
\overline{8} & \overline{9} & \overline{1} \\
\overline{1} & \overline{1} & \overline{1} \\
\overline{1} & \overline{1} & \overline{1} \\
\over$ **Example 1988**<br> **Example 1989**<br> **Example 1989**<br>
(canalicular) and basolateral domains (sinusoidal and lateral plasma membranes **CI**)<br> **CI**) and functional demarcation points between apical<br>
(canalicular) and basolateral domains (sinusoidal and<br>
lateral plasma membranes) of hepatocytes. These two<br>
membrane domains differ in their lipid composition<br>
(Meier et al (canalicular) and basolateral domains (sinusoidal and lateral plasma membranes) of hepatocytes. These two membrane domains differ in their lipid composition (Meier et al., 1984), and these differences are maintained by tig - proteins (Gumbiner, 1987). Tight junctions along with a) desmonstrated by tight junctions that are believed to provide<br>
and by tight junctions that are believed to provide<br>
effective barriers against lateral movement of lipids and<br>
gap-simulations at the lateral<br>
domain are i a) **. .** domain are important diffusional barriers between the desmosomes and gap-junctions present at the lateral<br>domain are important diffusional barriers between the<br>interstitium and bile. Tight junctions, because of their<br>permselectivity to cations (Bradley and Herz, 1978), proand the set of a set of  $\frac{4}{3}$ <br>  $\frac{4}{3}$ <br> and the street of their contents of the contents of the contents of the contents of the contents, particularly organic anions. In addition, and the contents, particularly organic anions. In addition, and the contents, part  $\frac{1}{2}$ <br>  $\frac{1}{2}$ <br> **EXECUTE IN SEX SECUTE IN SEXURE FOR SEXURE IN SEXURE FOR SEXURE THE I A TREATE TO BE THE CONFERENCE OF A TABLE THE CONFERENCE SUBARDING SU** Franchise Section of the Section of Section 1987;<br>
The Section of Section 1987;<br>
The Section of Section 1988; Phillips et<br>
The Section of Section 1988; Phillips et<br>
The Section of Section of electrolytes and water.<br>
The Se

al., 1986). Bile formed at the canaliculi is modified down-<br>stream in the bile ducts (ductular bile) by reabsorption<br>and/or secretion of electrolytes and water.<br>Active solute transport into canaliculi is primarily<br>responsi I-a)  $\sum_{k=1}^{\infty}$  and/or secretion of electrolytes and water.<br>
Active solute transport into canaliculi is primarily<br>
Active solute transport into canaliculi is primarily<br>
Reservation (Anwer, 1991;<br>
Arias et al., 1993; Me 1984). Of all the compounds in bile, bile acids are the most concentrated ones. It is now generally agreed that Active solute transport into canaliculi is primarily<br>
responsible for canalicular bile formation (Anwer, 1991;<br>
Arias et al., 1993; Meier, 1991; Klaassen and Watkins,<br>
20 high concentrated ones. It is now generally agreed **.** . **,- .-** major driving force for water movement during bile for- **1984**). Of all the compounds in bile, bile acids are the<br>  $\frac{36}{21}$   $\frac{36$ the conventionally defined as bile acid-dependent is conventionally defined as bile acid-dependent of the conventionally defined as bile acid-dependent of the conventionally defined as bile acid-dependent of the convention **ES a** consider the major driving force for water movement during bile for-<br> **ES a** dentile flow associated with bile acid<br> **ES a** dentile flow. However, even in the virtual absence of<br>  $\frac{1}{2}$  a dentile flow. However, e a)<br> **a)** C  $\overline{a}$ ,  $\overline{a}$ , **EXECUTE THE CONSULTER TRANSPARENT CONSULTER SERVICE IN A SURFACE OF**  $\frac{1}{2}$  **and**  $\frac{1}{2}$  **\frac{1}{2} . .** E- E **. .** bile flow versus bile acid excretion plot. The slope of the  $\frac{1}{2}$  and  $\frac{1}{2}$  a  $\begin{matrix}\n\text{a} & \text{b} & \text{c} & \text{d} & \text{d} & \text{c} & \text{d} & \text{e & \text{d}} \\
\text{c} & \text{d} & \text{e} & \text{e} & \text{f} & \text{f} & \text{f} & \text{f} & \text{f} \\
\text{d} & \text{e} & \text{f} & \text{f} & \text{f} & \text{f} & \text{f} \\
\text{e} & \text{f} & \text{f} & \text{f} & \text{f} & \text{f} \\
\text{f} & \text{f} & \text{f} & \text{f} & \text{f}$ regression line represents bile acid-dependent flow, and<br>is also a measure of the choleretic effect of bile acids (i.e.,<br>the increment in bile flow per increment in bile acid<br>excretion). In addition to bile acids, hormone **A)**  $\frac{3}{20}$   $\frac{3}{2$ 

 $\frac{1}{2}$   $\frac{1}{2}$  where the senecation of bile acid-independent bile flow (Er-<br>
bilger, 1988; Klaassen and Watkins, 1984; Moseley and<br>
Boyer, 1985; Boyer et al., 1992). Unequivocal evidence in<br>
digital active still lacking, and active<br>
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# 10 WATKINS AND SANDERS

**TABLE 4** *Effects of diabetes on hepatic glucuronidation reactions. All animals are rats unless otherwise noted. Animals are genetically diabetic or* **treated with strength warkling and SANDERS**<br>*thecuronidation reactions. All animals are rats unless otherwise noted. Animal*<br>*treated with streptozotocin (STZ) or alloxan as indicated to induce diabetes*<br>Increase



PHARMACOLOGICAL REVIEWS



provide an osmotic gradient, inasmuch as tight junctions<br>are readily permeable to these ions (Graf, 1983). Hepatransport of these inorganic ions may not be able to provide an osmotic gradient, inasmuch as tight junctions are readily permeable to these ions (Graf, 1983). Hepa-tocytes have a  $Na^+/H^+$  exchanger (Arias and Forgac, transport of these inorganic ions may not be able to<br>provide an osmotic gradient, inasmuch as tight junctions<br>are readily permeable to these ions (Graf, 1983). Hepa-<br>tocytes have a  $Na^+/H^+$  exchanger (Arias and Forgac,<br>19 transport of these inorganic ions may not be able<br>provide an osmotic gradient, inasmuch as tight junctia<br>are readily permeable to these ions (Graf, 1983). He<br>tocytes have a Na<sup>+</sup>/H<sup>+</sup> exchanger (Arias and Forg<br>1984; Mosel provide an osmotic gradient, inasmuch as tight junctions<br>are readily permeable to these ions (Graf, 1983). Hepa<br>tocytes have a Na<sup>+</sup>/H<sup>+</sup> exchanger (Arias and Forgac<br>1984; Moseley et al., 1986) and a Na<sup>+</sup>-HCO<sub>3</sub><sup>-</sup> cotra are readily permeable to these ions (Graf, 1983). Hepa-<br>tocytes have a Na<sup>+</sup>/H<sup>+</sup> exchanger (Arias and Forgac,<br>1984; Moseley et al., 1986) and a Na<sup>+</sup>-HCO<sub>3</sub><sup>-</sup> cotrans-<br>porter (Renner et al., 1989) on the sinusoidal memb tocytes have a Na<sup>+</sup>/H<sup>+</sup> exchanger (Arias and Forgac, 1984; Moseley et al., 1986) and a Na<sup>+</sup>-HCO<sub>3</sub><sup>-</sup> cotransporter (Renner et al., 1989) on the sinusoidal membrane, and a Cl<sup>-</sup>/HCO<sub>3</sub><sup>-</sup>(OH<sup>-</sup>) exchanger on the canali 1984; Moseley et al., 1986) and a Na<sup>+</sup>-HCO<sub>3</sub><sup>-</sup> cotrans-<br>porter (Renner et al., 1989) on the sinusoidal membrane, or<br>and a Cl<sup>-</sup>/HCO<sub>3</sub><sup>-</sup>(OH<sup>-</sup>) exchanger on the canalicular in<br>membrane (Meier et al., 1985). These ion porter (Renner et al., 1989) on the sinusoidal membrane,<br>and a Cl<sup>-</sup>/HCO<sub>3</sub><sup>-</sup>(OH<sup>-</sup>) exchanger on the canalicular<br>membrane (Meier et al., 1985). These ion transport<br>mechanisms, by regulating intracellular events, may afmembrane (Meier et al., 1985). These ion transport<br>mechanisms, by regulating intracellular events, may af-<br>fect biliary excretion of other osmotically active solutes<br>and thereby bile acid-independent flow. Biliary excre-<br>t membrane (meier et al., 1985). Inese ion transport<br>mechanisms, by regulating intracellular events, may af-<br>fect biliary excretion of other osmotically active solutes<br>and thereby bile acid-independent flow. Biliary excre-<br>t fect biliary excretion of other osmotically active solutes<br>and thereby bile acid-independent flow. Biliary excre-<br>tion of inorganic ions, in that case, may be mainly owing<br>to solvent drag and diffusion.<br>A number of organic

and thereby bile acid-independent flow. Biliary excretion of inorganic ions, in that case, may be mainly owing to solvent drag and diffusion.<br>A number of organic solutes (bilirubin, glutathione, amino acids) are concentrat and thereby bile acid-independent flow. Biliary excretion of inorganic ions, in that case, may be mainly owing<br>to solvent drag and diffusion.<br>A number of organic solutes (bilirubin, glutathione,<br>amino acids) are concentra to solvent drag and diffusion.<br>
A number of organic solutes (bilirubin, glutathione,<br>
amino acids) are concentrated in bile in addition to bile<br>
acids and could provide the osmotic gradient for bile<br>
formation. With the e to solvent drag and diffusion.<br>
A number of organic solutes (bilirubin, glutathione,<br>
amino acids) are concentrated in bile in addition to bile<br>
formation. With the exception of glutathione, the roles of<br>
other organic so A number of organic solutes (bilirubin, glutathione,<br>amino acids) are concentrated in bile in addition to bile<br>acids and could provide the osmotic gradient for bile<br>formation. With the exception of glutathione, the roles amino acids) are concentrated in bile in addition to bile<br>acids and could provide the osmotic gradient for bile<br>formation. With the exception of glutathione, the roles of<br>other organic solutes in bile acid-independent bile acids and could provide the osmotic gradient for bile<br>formation. With the exception of glutathione, the roles of<br>other organic solutes in bile acid-independent bile flow<br>are unclear. There is growing evidence that biliary formation. With the exception of glutathione, the roles of other organic solutes in bile acid-independent bile flow are unclear. There is growing evidence that biliary excretion of glutathione and its conjugates may be inv other organic solutes in bile acid-independent bile flow<br>are unclear. There is growing evidence that biliary ex-<br>cretion of glutathione and its conjugates may be in-<br>volved in bile acid-independent flow. Agents that in-<br>cr are unclear. There is growing evidence that biliary excretion of glutathione and its conjugates may be in-<br>volved in bile acid-independent flow. Agents that in-<br>crease or decrease glutathione excretion have similar me-<br>eff

Truong, 1989; Brigelius and Anwer, 1981; Hoener et al., Truong, 1989; Brigelius and Anwer, 1981; Hoener et al.,<br>1989). As in the case of bile acids, canalicular bile flow is<br>linearly related to biliary excretion of glutathione and is Truong, 1989; Brigelius and Anwer, 1981; Hoener et al.,<br>1989). As in the case of bile acids, canalicular bile flow is<br>linearly related to biliary excretion of glutathione and is<br>not abolished when glutathione excretion is Truong, 1989; Brigelius and Anwer, 1981; Hoener et<br>1989). As in the case of bile acids, canalicular bile flow<br>linearly related to biliary excretion of glutathione and<br>not abolished when glutathione excretion is extra<br>lated Truong, 1989; Brigelius and Anwer, 1981; Hoener et al., 1989). As in the case of bile acids, canalicular bile flow is linearly related to biliary excretion of glutathione and is not abolished when glutathione excretion is 1989). As in the case of bile acids, canalicular bile flow is linearly related to biliary excretion of glutathione and into abolished when glutathione excretion is extrapolated to zero (Ballatori and Truong, 1989). Thus, s linearly related to biliary excretion of glutathione and into abolished when glutathione excretion is extrapolated to zero (Ballatori and Truong, 1989). Thus, solute other than glutathione may also be involved in bile acid not abolished when glutathione excretion is extrapo-<br>lated to zero (Ballatori and Truong, 1989). Thus, solutes<br>other than glutathione may also be involved in bile acid-<br>independent bile flow. It is conceivable that the com lated to zero (Ballatori and Truong, 1989). Thus, solumble of the photon of the acid-independent bile flow. It is conceivable that the coordinated osmotic activity of a number of organic solumn excreted into bile contribut other than glutathione may also be involved in bile acid-<br>independent bile flow. It is conceivable that the com-<br>bined osmotic activity of a number of organic solutes<br>excreted into bile contributes to bile acid-independen independent bile flow. It is conceivable that the com-<br>bined osmotic activity of a number of organic solutes<br>excreted into bile contributes to bile acid-independent<br>flow. The contribution of each solute, however, may be<br>ap bined osmotic activity of a number of organic solute<br>excreted into bile contributes to bile acid-independen<br>flow. The contribution of each solute, however, may b<br>apparent only under experimental conditions designe<br>to enhan creted into bile contributes to bile acid-independent<br>w. The contribution of each solute, however, may be<br>parent only under experimental conditions designed<br>enhance biliary excretion of that particular solute.<br>A large numb

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flow. The contribution of each solute, however, may be<br>apparent only under experimental conditions designed<br>to enhance biliary excretion of that particular solute.<br>A large number of exogenous organic compounds that<br>are con are concentrated in bile also increase canalicular bile<br>formation (Klaassen and Watkins, 1984). These com-<br>pounds can induce choleresis by direct osmotic effects, to enhance biliary excretion of that particular solute.<br>A large number of exogenous organic compounds that<br>are concentrated in bile also increase canalicular bile<br>formation (Klaassen and Watkins, 1984). These com-<br>pounds A large number of exogenous organic compounds that<br>are concentrated in bile also increase canalicular bile<br>formation (Klaassen and Watkins, 1984). These com-<br>pounds can induce choleresis by direct osmotic effects,<br>by incr are concentrated in bile also increase canalicular bile<br>formation (Klaassen and Watkins, 1984). These com-<br>pounds can induce choleresis by direct osmotic effects,<br>by increasing biliary  $HCO_3^-$  excretion, or by inhibiting<br> formation (Klaassen and Watkins, 1984). These compounds can induce choleresis by direct osmotic effect<br>by increasing biliary  $HCO_3^-$  excretion, or by inhibitin<br>reabsorption of electrolytes and fluid from canalicu<br>(Anwer, pounds can induce choleresis by direct osmotic effects,<br>by increasing biliary  $HCO_3^-$  excretion, or by inhibiting<br>reabsorption of electrolytes and fluid from canaliculi<br>(Anwer, 1985; Anwer and Hegner, 1982, 1983a,b). Howmechanism.



DIABETES MELLITUS AND HEPATOBILIARY FUNCTION<br>TABLE 5<br>*Effects of diabetes on hepatic glutathione S-transferase. All animals used are rats unless otherwise noted; animals are genetically diabetic<br><i>or treated with streptozot* 

synthesis, regulate enzyme function (either directly or changes in membrane potential (Wondergem, 1983). Boindirectly via glucose or some other metabolic agent), lus intravenous injections of insulin into normal dogs and c indirectly via glucose or some other metabolic agent), lus intravenous injections of insulin into normal dogs<br>and control carbohydrate metabolism (Porte and Halter, (Jones and Meyers, 1979) and diabetic rats (Villanueva<br>19 and control carbohydrate metabolism (Porte and Halter, (Jones and Meyers, 1979) and diabetic rats (Villanueva<br>1981). Moreover, insulin infusion produces a significant et al., 1990b) stimulate bile acid excretion and reduce 1981). Moreover, insulin infusion produces a significant et al., 1990b) stimulate bile acid excretion and reduce<br>choleresis (increased bile flow rate) in normal dogs (Aus-<br>tin et al., 1977; Garberoglio et al., 1983; Jones choleresis (increased bile flow rate) in normal dogs (Aus-<br>tin et al., 1977; Garberoglio et al., 1983; Jones, 1976; influence hepatic uptake and biliary excretion is poorly<br>Jones and Meyers, 1979; Snow and Jones, 1978) or in et al., 1977; Garberoglio et al., 1983; Jones, 1976; influence hepatic uptake and biliary excretion is poor<br>Jones and Meyers, 1979; Snow and Jones, 1978) or rats understood.<br>(Thomsen and Larsen, 1982a,b), apparently by

*Pichloronitrobenzene*<br>*B. Insulin- and Diabetes-induced Alterations in Bile* al., 1984). This effect may be secondary to stimulation of *Production and Flow* sinusoidal Na<sup>+</sup>-K<sup>+</sup>-ATPase (Thomsen, 1983; Thomsen Insulin a Insulin- and Diabetes-induced Alterations in Bile al., 1984). This effect may be secondary to stimulation of<br>
coduction and Flow sinusoidal Na<sup>+</sup>-K<sup>+</sup>-ATPase (Thomsen, 1983; Thomsen<br>
Insulin acts in numerous ways to promot B. Insulin- and Diabetes-induced Alterations in Bile al., 1984). This effect may be secondary to stimulation of<br>
Production and Flow sinusoidal Na<sup>+</sup>-K<sup>+</sup>-ATPase (Thomsen, 1983; Thomsen<br>
Insulin acts in numerous ways to p Froduction and Flow sinusoidal Na<sup>+</sup>-K<sup>+</sup>-ATPase (Thomsen, 1983; Thomsen<br>Insulin acts in numerous ways to promote protein and Larsen, 1982a; Gelehrter et al., 1984) as well as<br>synthesis, regulate enzyme function (either d and control carbohydrate metabolism (Porte and Halter, and Meyers, 1979) and diabetic rats (Villanueva<br>
and control carbohydrate metabolism (Porte and Halter, discussions of insulin into normal dogs<br>
and control carbohydra Insulin acts in numerous ways to promote protein<br>synthesis, regulate enzyme function (either directly or<br>indirectly via glucose or some other metabolic agent),<br>and control carbohydrate metabolism (Porte and Halter, (Jones

 $\begin{array}{ll}\n\text{e} & \text{b} & \text{b} \\
\text{e} & \text{b} & \text{b} \\
\text{f} & \text{d} & \text{d} \\
\text{f} & \text{f} & \text{d} \\
\text{g} & \text{f} & \text{d} \\
\text{g} & \text{f} & \text{d} \\
\text{h} & \text{h} & \text{h} \\
\text{h} & \text{h} & \text$ 

*Effect of time after diabetogenesis on bile flow (Jones, R. S., et* betes are indicated in table 6. Flow is depressed im<br>*Effect of time after diabetogenesis on bile flow (* $\mu$ */min/g liver). All animals used are male Wist* 

TABLE 6 Effect of time after diabetogenesis on bile flow ( $\mu/min/g$ liver). All animals used are male Wistar or Sprague-Dawley (SD) rats as indicated										
Rats	STZ/alx	Time	Anesthetic	Control	<b>Diabetic</b>	% Control	<b>Source</b>			
Wistar	<b>STZ</b>	1 day		0.9	0.45	50	Andrews and Griffiths, 1984			
Wistar	STZ	1 day	pentobarbital	$2.5\,$	$1.6\phantom{0}$	64	Carnovale et al., 1987			
Wistar	STZ	1 day	pentobarbital	2.3	1.6	64	Carnovale et al., 1986			
Wistar	<b>STZ</b>	1 day	pentobarbital	2.38	1.21	51	Carnovale and Rodriguez-Garay, 1984			
		7 day			1.38	58				
		15 day			1.72	72				
Wistar	<b>STZ</b>	1 day	pentobarbital	1.9	1.2	63	Marin et al., 1988			
		3 day			1.35	71				
		6 day			1.4	74				
		20 day			1.6	84				
<b>Wistar</b>	<b>STZ</b>	4 day	urethane	1.72	1.15	67	Siegers et al., 1979			
SD	<b>STZ</b>	$21$ day	ether	0.87	1.97	236	Kirkpatrick and Kraft, 1984			
SD	<b>STZ</b>	30 day	urethane	1.35	1.60	119	Watkins and Dykstra, 1987			
SD	<b>STZ</b>	30 day	urethane	1.63	1.60	98	Watkins and Noda, 1986			
SD	<b>STZ</b>	7 day	urethane	1.77	1.21	68	Watkins and Sanders (unpubl.)			
		14 day			1.28	72				
		30 day			1.87	106				
Wistar	alloxan	30 day	pentobarbital	1.80	1.75	97	Badawy and Evans, 1977			

12 waTKINS /<br>diately after diabetogen administration but seems nor-<br>mal 4 weeks later. It is likely, however, that the waTKINS AND S<br>diately after diabetogen administration but seems nor-<br>mal 4 weeks later. It is likely, however, that the bil<br>diabetogen itself is toxic to the liver, causing decreases fac WATKINS AN<br>diately after diabetogen administration but seems nor-<br>mal 4 weeks later. It is likely, however, that the<br>diabetogen itself is toxic to the liver, causing decreases<br>in bile flow and in biliary excretion of sever The flately after diabetogen administration but seems normal 4 weeks later. It is likely, however, that the diabetogen itself is toxic to the liver, causing decreases in bile flow and in biliary excretion of several compou diately after diabetogen administration but seems n<br>mal 4 weeks later. It is likely, however, that t<br>diabetogen itself is toxic to the liver, causing decreas<br>in bile flow and in biliary excretion of several compoun<br>for the mal 4 weeks later. It is likely, however, that the diabetogen itself is toxic to the liver, causing decreases in bile flow and in biliary excretion of several compounds for the first 15 to 20 days after administration (Car diabetogen itself is toxic to the liver, causing decreases fact<br>in bile flow and in biliary excretion of several compounds class<br>for the first 15 to 20 days after administration (Carno-<br>vale and Rodriguez-Garay, 1984; Carn in bile flow and in biliary excretion of several compounds<br>for the first 15 to 20 days after administration (Carno-<br>vale and Rodriguez-Garay, 1984; Carnovale et al., 1987,<br>1991; Chawalit et al., 1982). Both biliary excreti for the first 15 to 20 days after administration (Carnovale and Rodriguez-Garay, 1984; Carnovale et al., 1987, 1991; Chawalit et al., 1982). Both biliary excretion and bile flow return to normal levels by 28 to 30 days aft vale and Rodriguez-Garay, 1984; Carnovale et al., 1987, st<br>1991; Chawalit et al., 1982). Both biliary excretion and in<br>bile flow return to normal levels by 28 to 30 days after<br>streptozotocin or alloxan (Uchida et al., 1979 1991; Chawalit et al., 1982). Both biliary excretion a<br>bile flow return to normal levels by 28 to 30 days aft<br>streptozotocin or alloxan (Uchida et al., 1979; Watki<br>and Dykstra, 1987; Watkins and Noda, 1986), in spite<br>the c bile flow return to normal levels by 28 to 30 days a<br>streptozotocin or alloxan (Uchida et al., 1979; Watk<br>and Dykstra, 1987; Watkins and Noda, 1986), in spit<br>the continued presence of hypoinsulinemia and hy<br>glycemia. In ra streptozotocin or alloxan (Uchida et al., 1979; Watkins cause and Dykstra, 1987; Watkins and Noda, 1986), in spite of the continued presence of hypoinsulinemia and hyper-<br>glycemia. In rats treated with nicotinamide, strep the continued presence of hypoinsulinemia and hyper-<br>glycemia. In rats treated with nicotinamide, streptozo-<br>tocin loses its diabetogenic properties but continues to<br>decrease bile flow and bile acid output (Carnovale et al 1987).

tocin loses its diabetogenic properties but continues to decrease bile flow and bile acid output (Carnovale et al., 1987).<br>1987). Some workers report bile flow in terms of flow per kg<br>body weight, whereas others report flo decrease bile flow and bile acid output (Carnovale et al.,  $2x$ , 1987).<br>
Some workers report bile flow in terms of flow per kg potentially different interpretations of the pure same data. Because of liver hypertrophy, liv 1987).<br>Some workers report bile flow in terms of flow per kg<br>body weight, whereas others report flow per gram liver,<br>resulting in potentially different interpretations of the<br>same data. Because of liver hypertrophy, liver Some workers report bile flow in terms of flow per kg poody weight, whereas others report flow per gram liver, the resulting in potentially different interpretations of the pusame data. Because of liver hypertrophy, liver body weight, whereas others report flow per gram li<br>resulting in potentially different interpretations of<br>same data. Because of liver hypertrophy, liver weig<br>body weight ratios in diabetic rats may be more t<br>20% higher tha resulting in potentially different interpretations of the pussume data. Because of liver hypertrophy, liver weight/ 199<br>body weight ratios in diabetic rats may be more than 199<br>20% higher than in weight-matched controls. S same data. Because of liver hypertrophy, liver weight body weight ratios in diabetic rats may be more the 20% higher than in weight-matched controls. Streptoz tocin- and alloxan-induced diabetic animals fail to ga weight a body weight ratios in diabetic rats may be more than<br>20% higher than in weight-matched controls. Streptozo-<br>tocin- and alloxan-induced diabetic animals fail to gain<br>weight as fast as normals, leading to even larger differtocin- and alloxan-induced diabetic animals fail to gain<br>weight as fast as normals, leading to even larger differ-<br>ences in the liver weight/body weight ratios of age-<br>matched pairs. Bile flow rates 7, 14, and 30 days afte weight as fast as normals, leading to even larger differences in the liver weight/body weight ratios of a matched pairs. Bile flow rates 7, 14, and 30 days aftereptozotocin, when calculated in nmol/min/gram liv were 68%, 7 ences in the liver weight/body weight ratios of age-<br>matched pairs. Bile flow rates 7, 14, and 30 days after<br>streptozotocin, when calculated in nmol/min/gram liver,<br>were 68%, 72%, and 106% of normal bile flow, respec-<br>tive matched pairs. Bile flow rates 7, 14, and 30 days after sufferent extreptozotocin, when calculated in nmol/min/gram liver, in were 68%, 72%, and 106% of normal bile flow, respectively (Watkins and Sanders, 1991). However, streptozotocin, when calculated in nmol/min/gram liver, in the were 68%, 72%, and 106% of normal bile flow, respectively (Watkins and Sanders, 1991). However, when cal-<br>tively (Watkins and Sanders, 1991). However, when cal were 68%, 72%, and 106% of normal bile flow, respectively (Watkins and Sanders, 1991). However, when calculated in nmol/min/kg body weight, these figures were can calculated in nmol/min/kg body weight, these figures were tively (Watkins and Sanders, 1991). H<br>culated in nmol/min/kg body weight, 1<br>85%, 94%, and 130% of normal bile<br>support the theory that long-term d<br>little adverse effect on bile formation.<br>Decreased bile flow in diabetic rat lated in nmol/min/kg body weight, these figures were ca<br>
%, 94%, and 130% of normal bile flow, seeming to after the theory that long-term diabetes may have entitle adverse effect on bile formation.<br>
Decreased bile flow in

support the theory that long-term diabetes may have<br>little adverse effect on bile formation.<br>Decreased bile flow in diabetic rats may be a result of<br>the cholestatic factors hyperglycemia and hypoinsuline-<br>mia rather than w Decreased bile flow in diabetic rats may be a result of<br>the cholestatic factors hyperglycemia and hypoinsuline-<br>mia rather than water or electrolyte imbalance or gen-<br>eralized damage to the hepatic secretory system (Ackerlittle adverse effect on bile formation.<br>Decreased bile flow in diabetic rats may be a result<br>the cholestatic factors hyperglycemia and hypoinsulin<br>mia rather than water or electrolyte imbalance or ge<br>eralized damage to th Decreased bile flow in diabetic rats may be a result of fite cholestatic factors hyperglycemia and hypoinsuline-<br>mia rather than water or electrolyte imbalance or gen-<br>eralized damage to the hepatic secretory system (Acker the cholestatic factors hyperglycemia and hypoinsuline-<br>mia rather than water or electrolyte imbalance or gen-<br>eralized damage to the hepatic secretory system (Acker-<br>man and Leibman, 1977; Marin et al., 1988). Induction<br>o mia rather than water or electrolyte imbalance or generalized damage to the hepatic secretory system (Ackerman and Leibman, 1977; Marin et al., 1988). Induction of hyperglycemia by infusion of glucose produces cholestasis eralized damage to the hepatic secretory system (Ackerman and Leibman, 1977; Marin et al., 1988). Induction<br>of hyperglycemia by infusion of glucose produces cho-<br>lestasis (Guzelian and Boyer, 1974; Zahavi et al., 1985),<br>ap man and Leibman, 1977; Marin et al., 1988). Induction evolution of hyperglycemia by infusion of glucose produces cholest<br>asis (Guzelian and Boyer, 1974; Zahavi et al., 1985), tail apparently at the canalicular level (Muno of hyperglycemia by infusion of glucose produces cho-<br>lestasis (Guzelian and Boyer, 1974; Zahavi et al., 1985), tail<br>apparently at the canalicular level (Munoz et al., 1986). has<br>Glucose infusion also leads to decreased s lestasis (Guzelian and Boyer, 1974; Zahavi et al., 1985), tain<br>apparently at the canalicular level (Munoz et al., 1986). have<br>Glucose infusion also leads to decreased secretion of bile<br>crisis and electrolytes, such as  $Na^$ apparently at the canalicular level (Munoz et al., 1986).<br>Glucose infusion also leads to decreased secretion of bile<br>acids and electrolytes, such as  $Na^+$ ,  $K^+$ ,  $Cl^-$ , and<br> $HCO_3^-$ , increased hepatic levels of UDP-glucose Glucose infusion also leads to decreased secretion of bile cacids and electrolytes, such as  $Na^+$ ,  $K^+$ ,  $Cl^-$ , and sl<br>HCO<sub>3</sub><sup>-</sup>, increased hepatic levels of UDP-glucose and tactivity of bilirubin glucuronyltransferase, a acids and electrolytes, such as  $Na^+$ ,  $K^+$ ,  $Cl^-$ , and  $HCO_3^-$ , increased hepatic levels of UDP-glucose and activity of bilirubin glucuronyltransferase, and in creased conjugation and biliary excretion of bilirubin (Muno  $HCO_3^-$ , increased hepatic levels of UDP-glucose and tactivity of bilirubin glucuronyltransferase, and increased conjugation and biliary excretion of bilirubin comparate (Munoz et al., 1986, 1987). In addition, Olson and activity of bilirubin glucuronyltransferase, and increased conjugation and biliary excretion of bilirubin con<br>(Munoz et al., 1986, 1987). In addition, Olson and Fuji-<br>moto (1980) demonstrate a highly selective glucose izz<br> creased conjugation and biliary excretion of bilirubin<br>(Munoz et al., 1986, 1987). In addition, Olson and Fuji-<br>poimoto (1980) demonstrate a highly selective glucose izs<br>transporter in the biliary tree that returns glucose (Munoz et al., 1986, 1987). In addition, Olson and Fuji-<br>moto (1980) demonstrate a highly selective glucose<br>transporter in the biliary tree that returns glucose to the<br>liver, keeping biliary glucose concentration lower tha moto (1980) demonstrate a highly selective glucose transporter in the biliary tree that returns glucose to the liver, keeping biliary glucose concentration lower than that in plasma, even during hyperglycemia. Moreover, hy transporter in the biliary tree that returns glucose to the of solu<br>liver, keeping biliary glucose concentration lower than port n<br>that in plasma, even during hyperglycemia. Moreover, other  $\alpha$ <br>hyperosmotic cell swelling liver, keeping biliary glucose concentration lower than<br>that in plasma, even during hyperglycemia. Moreover,<br>hyperosmotic cell swelling stimulates both taurocholate<br>secretion into bile and bile acid-dependent bile flow<br>(Ha that in plasma, even during hyperglycemia. Moreover,<br>hyperosmotic cell swelling stimulates both taurocholate<br>secretion into bile and bile acid-dependent bile flow<br>(Hallbrucker et al., 1992). However, metabolic and iso-<br>top hyperosmotic cell swelling stimulates both taurocholate<br>secretion into bile and bile acid-dependent bile flow<br>(Hallbrucker et al., 1992). However, metabolic and iso-<br>topic dilution studies indicate that there may be intrasecretion into bile and bile acid-dependent bile flow ula<br>(Hallbrucker et al., 1992). However, metabolic and iso-<br>boyic dilution studies indicate that there may be intra-<br>cellular dehydration in rats treated 14 days before (Hallbrucker et al., 1992). However, metabolic and isotopic dilution studies indicate that there may be intracellular dehydration in rats treated 14 days before experimentation with streptozotocin (Anwana and is Garland,

canalicular bile formation. Thus, conflicting effects on bile SANDERS<br>canalicular bile formation. Thus, conflicting effects on<br>bile flow may be obtained when the so-called cholestatic<br>factors of hyperglycemia and intracellular dehydration Factors of SANDERS<br>canalicular bile formation. Thus, conflicting effects on<br>bile flow may be obtained when the so-called cholestatic<br>factors of hyperglycemia and intracellular dehydration<br>clash with the choleretic effect o canalicular bile formation. Thus, conflicting effects on<br>bile flow may be obtained when the so-called cholestatic<br>factors of hyperglycemia and intracellular dehydration<br>clash with the choleretic effect of increased bile ac canalicular bile formation. Thus, conflicting effects on<br>bile flow may be obtained when the so-called cholestatic<br>factors of hyperglycemia and intracellular dehydration<br>clash with the choleretic effect of increased bile ac bile flow may be obtained when the so-called cholest:<br>factors of hyperglycemia and intracellular dehydrat<br>clash with the choleretic effect of increased bile  $\varepsilon$ <br>(especially taurocholate) transport. Obviously, fut<br>studies factors of hyperglycemia and intracellular dehydration<br>clash with the choleretic effect of increased bile acid<br>(especially taurocholate) transport. Obviously, future<br>studies must examine these conflicting data on diabetes-(especially taurocholate) transport. Obviously, future<br>studies must examine these conflicting data on diabetes-<br>induced changes in bile flow rate, as well as address the<br>question of whether or not streptozotocin and alloxa studies must examine these conflicting data on diabetes-

# \rll. Diabetes and Biliary Excretion

# *A. General Considerations Regarding Hepatobiliary Excretion*

1987).<br>
Some workers report bile flow in terms of flow per kg<br>
body weight, whereas others report flow per gram liver, the intact liver, isolated liver parenchymal cells, and<br>
resulting in potentially different interpretat tocin- and alloxan-induced diabetic animals fail to gain an experimental model for studies on bile acid secretion, weight as fast as normals, leading to even larger differ-<br>ences in the liver weight/body weight ratios of a port is derived from three distinct experimental models: A. General Considerations Regarding Hepatobiliary<br>Excretion<br>Current knowledge of canalicular membrane trans-<br>port is derived from three distinct experimental models:<br>the intact liver, isolated liver parenchymal cells, and A. General Considerations Regarding Hepdobitiary<br>Excretion<br>Current knowledge of canalicular membrane trans-<br>port is derived from three distinct experimental models:<br>the intact liver, isolated liver parenchymal cells, and<br>p Excretion<br>Current knowledge of canalicular membrane trans-<br>port is derived from three distinct experimental models:<br>the intact liver, isolated liver parenchymal cells, and<br>purified canalicular membrane vesicles (Arias et a Current knowledge of canalicular membrane trans-<br>port is derived from three distinct experimental models:<br>the intact liver, isolated liver parenchymal cells, and<br>purified canalicular membrane vesicles (Arias et al.,<br>1993; port is derived from three distinct experimental models:<br>the intact liver, isolated liver parenchymal cells, and<br>purified canalicular membrane vesicles (Arias et al.,<br>1993; Boyer et al., 1992; Kukongviriyapan and Stacey,<br>1 the intact liver, isolated liver parenchymal cells, and<br>purified canalicular membrane vesicles (Arias et al.,<br>1993; Boyer et al., 1992; Kukongviriyapan and Stacey,<br>1991; Petzinger, 1991; Siegers, 1991; Wisher and Evans,<br>19 purified canalicular membrane vesicles (Arias et al., 1993; Boyer et al., 1992; Kukongviriyapan and Stacey, 1991; Petzinger, 1991; Siegers, 1991; Wisher and Evans, 1975). Isolated hepatocytes have often been neglected as a 1993; Boyer et al., 1992; Kukongviriyapan and Stac<br>1991; Petzinger, 1991; Siegers, 1991; Wisher and Eva<br>1975). Isolated hepatocytes have often been neglected<br>an experimental model for studies on bile acid secreti<br>although 1991; Petzinger, 1991; Siegers, 1991; Wisher and Evans<br>1975). Isolated hepatocytes have often been neglected a<br>an experimental model for studies on bile acid secretion<br>although the intact organ allows only indirect observa 1975). Isolated hepatocytes have often been neglected as<br>an experimental model for studies on bile acid secretion,<br>although the intact organ allows only indirect observa-<br>tions of canalicular transport physiology. Direct m an experimental model for studies on bile acid secretion<br>although the intact organ allows only indirect observa<br>tions of canalicular transport physiology. Direct mea<br>surement of canalicular carrier function is accomplished although the intact organ allows only indirect obser<br>tions of canalicular transport physiology. Direct m<br>surement of canalicular carrier function is accomplis<br>in the membrane vesicles using specific indicator  $\alpha$ <br>pounds t tions of canalicular transport physiology. Direct measurement of canalicular carrier function is accomplished<br>in the membrane vesicles using specific indicator com-<br>pounds that serve as markers for secretion. Unfortu-<br>nate surement of canalicular carrier function is accomplished<br>in the membrane vesicles using specific indicator com-<br>pounds that serve as markers for secretion. Unfortu-<br>nately, transport studies using basolateral-enriched and<br> in the membrane vesicles using specific indicator compounds that serve as markers for secretion. Unfortunately, transport studies using basolateral-enriched and canalicular-enriched plasma membrane vesicles may be affected pounds that serve as markers for secretion. Unfortunately, transport studies using basolateral-enriched and canalicular-enriched plasma membrane vesicles may be affected by diabetes-induced alterations in membrane environm nately, transport studies using basolateral-enriched and<br>canalicular-enriched plasma membrane vesicles may be<br>affected by diabetes-induced alterations in membrane<br>environment, which may affect membrane isolation and<br>purity canalicular-enriched plasma membrane vesicles may be<br>affected by diabetes-induced alterations in membrane<br>environment, which may affect membrane isolation and<br>purity. These valid concerns, however, should not hinder<br>future affected by diabetes-induced alterations in membrane<br>environment, which may affect membrane isolation and<br>purity. These valid concerns, however, should not hinder<br>future efforts to apply this technology to membrane<br>transpo environment, which may affect membrane isolation and<br>purity. These valid concerns, however, should not hinder<br>future efforts to apply this technology to membrane<br>transport studies. Finally, the intact organ should be the<br>b purity. These valid concerns, however, should not hindefuture efforts to apply this technology to membrane transport studies. Finally, the intact organ should be the bile canaliculus; how secretion of compounds into the bi future efforts to apply this technology to membrane<br>transport studies. Finally, the intact organ should be the<br>best model to analyze bile formation and to study the<br>secretion of compounds into the bile canaliculus; how-<br>ev transport studies. Finally, the intact organ should be the best model to analyze bile formation and to study the secretion of compounds into the bile canaliculus; however, attempts to sample canalicular bile in vivo have f best model to analyze bile formation and to study the secretion of compounds into the bile canaliculus; how-<br>ever, attempts to sample canalicular bile in vivo have<br>failed. Recently, bile canaliculi of hepatocytes main-<br>tai secretion of compounds into the bile canaliculus; how-<br>ever, attempts to sample canalicular bile in vivo have<br>failed. Recently, bile canaliculi of hepatocytes main-<br>tained as monolayer cultures on a gas-permeable foil<br>have failed. Recently, bile canaliculi of hepatocytes maintained as monolayer cultures on a gas-permeable foil have been punctured and primary bile collected by micropipette (Petzinger et al., 1989b). This technique should offe tained as monolayer cultures on a gas-permeable foil<br>have been punctured and primary bile collected by mi-<br>cropipette (Petzinger et al., 1989b). This technique<br>should offer direct measurements of primary bile con-<br>tents in tents in the near future. we been punctured and primary bile collected by mi-<br>opipette (Petzinger et al., 1989b). This technique<br>ould offer direct measurements of primary bile con-<br>nts in the near future.<br>Canalicular transport events can be divided

cropipette (Petzinger et al., 1989b). This technique should offer direct measurements of primary bile contents in the near future.<br>Canalicular transport events can be divided into thromponents: physical diffusion, carriershould offer direct measurements of primary bile contents in the near future.<br>Canalicular transport events can be divided into three components: physical diffusion, carrier-mediated transport, and vesicular endocytosis or tents in the near future.<br>Canalicular transport events can be divided into three<br>components: physical diffusion, carrier-mediated trans-<br>port, and vesicular endocytosis or exocytosis. The local-<br>ization of ATP-driven pumps Canalicular transport events can be divided into three components: physical diffusion, carrier-mediated transport, and vesicular endocytosis or exocytosis. The localization of ATP-driven pumps, together with the direction components: physical diffusion, carrier-mediated trans-<br>port, and vesicular endocytosis or exocytosis. The local-<br>ization of ATP-driven pumps, together with the direction<br>of solute transport by sodium-driven symport and an port, and vesicular endocytosis or exocytosis. The localization of ATP-driven pumps, together with the direction<br>of solute transport by sodium-driven symport and anti-<br>port mechanisms, indicate that the liver shares with<br>o ization of ATP-driven pumps, together with the direction<br>of solute transport by sodium-driven symport and anti<br>port mechanisms, indicate that the liver shares with<br>other epithelia, such as kidney and intestine, common<br>tran of solute transport by sodium-driven symport and anti-<br>port mechanisms, indicate that the liver shares with<br>other epithelia, such as kidney and intestine, common<br>transport mechanisms with similar interplay and mod-<br>ulation port mechanisms, indicate that the liver shares with<br>other epithelia, such as kidney and intestine, common<br>transport mechanisms with similar interplay and mod-<br>ulation (Kinne, 1987; Meier, 1988, 1989; Moseley and<br>Boyer, 19 other epithelia, such as kidney and intestine, common<br>transport mechanisms with similar interplay and mod-<br>ulation (Kinne, 1987; Meier, 1988, 1989; Moseley and<br>Boyer, 1985; Zimniak and Awasthi, 1993). Compounds<br>are secrete transport mechanisms with similar interplay and modulation (Kinne, 1987; Meier, 1988, 1989; Moseley and Boyer, 1985; Zimniak and Awasthi, 1993). Compounds are secreted vectorially out of hepatic cytosol directly into bile. ulation (Kinne, 1987; Meier, 1988, 1989; Moseley and<br>Boyer, 1985; Zimniak and Awasthi, 1993). Compounds<br>are secreted vectorially out of hepatic cytosol directly<br>into bile. Although the direction of the secretion process<br>is Boyer, 1985; Zimniak and Awasthi, 1993). Compounds<br>are secreted vectorially out of hepatic cytosol directly<br>into bile. Although the direction of the secretion process<br>is in principle fixed, some compounds can reflux back<br>i

PHARMACOLOGICAL REVIEW



DIABETES MELLITUS AND HEPATOBILIARY FUNCTION <sup>13</sup>

DIABETES MELLITUS AND HEP.<br>Boyer, 1974; Jones, A. L., et al., 1984). Once within the see<br>hepatocyte, a compound may also be secreted back into cre DIABETES MELLITUS AND HEPA<br>Boyer, 1974; Jones, A. L., et al., 1984). Once within the sen<br>hepatocyte, a compound may also be secreted back into cre<br>the blood stream across the sinusoidal membrane. This pro DIABETES MELLITUS AND HEI<br>Boyer, 1974; Jones, A. L., et al., 1984). Once within the<br>hepatocyte, a compound may also be secreted back into<br>the blood stream across the sinusoidal membrane. This<br>reflux bypassing of the canali Boyer, 1974; Jones, A. L., et al., 1984). Once within the hepatocyte, a compound may also be secreted back into the blood stream across the sinusoidal membrane. This reflux bypassing of the canalicular membrane is increase hepatocyte, a compound may also be secreted back into<br>the blood stream across the sinusoidal membrane. This<br>reflux bypassing of the canalicular membrane is in-<br>creased in cholestasis. Under those circumstances, hepatocyte, a compound may also be secreted back in<br>the blood stream across the sinusoidal membrane. Thi<br>reflux bypassing of the canalicular membrane is ir<br>creased in cholestasis. Under those circumstance:<br>canalicular tran the blood stream across the sinusoidal membrane. This perflux bypassing of the canalicular membrane is increased in cholestasis. Under those circumstances, to canalicular transport proteins may redistribute to basotiateral reflux bypassing of the canalicular membrane is<br>creased in cholestasis. Under those circumstar<br>canalicular transport proteins may redistribute to l<br>lateral membrane areas, and this sinusoidal secre<br>may even exceed biliary eased in cholestasis. Under those circumstances,<br>nalicular transport proteins may redistribute to baso-<br>teral membrane areas, and this sinusoidal secretion<br>ay even exceed biliary elimination (Sies, 1989).<br>Recent reviews of

canalicular transport proteins may redistribute to baso-<br>lateral membrane areas, and this sinusoidal secretion<br>may even exceed biliary elimination (Sies, 1989).<br>Recent reviews of transport studies with canalicular<br>vesicles lateral membrane areas, and this sinusoidal secretion ti<br>may even exceed biliary elimination (Sies, 1989). pl<br>Recent reviews of transport studies with canalicular in<br>vesicles have suggested that an interplay of primary, in may even exceed biliary elimination (Sies, 1989).<br>Recent reviews of transport studies with canalicular<br>vesicles have suggested that an interplay of primary,<br>secondary, and tertiary transport mechanisms sustain<br>canalicular Recent reviews of transport studies with canalicular invesicles have suggested that an interplay of primary, intercondary, and tertiary transport mechanisms sustain representation (Arias et al., 1993; Meier, tion 1988, 198 vesicles have suggested that an interplay of primary, in secondary, and tertiary transport mechanisms sustain recanalicular bile secretion (Arias et al., 1993; Meier, tion 1988, 1989). Primary transport systems utilize the canalicular bile secretion (Arias et al., 1993; Meier, tion 1988, 1989). Primary transport systems utilize the mar<br>chemical energy of ATP hydrolysis by ATPases to drive 3-0<br>uphill transmembrane solute transport (Arias, 19 1988, 1989). Primary transport systems utilize t<br>chemical energy of ATP hydrolysis by ATPases to dri<br>uphill transmembrane solute transport (Arias, 196<br>Zimniak and Awasthi, 1993). ATP splitting activity<br>the canaliculus and chemical energy of ATP hydrolysis by ATPases to drive<br>uphill transmembrane solute transport (Arias, 1989; cr<br>Zimniak and Awasthi, 1993). ATP splitting activity in to<br>the canaliculus and bile ducts is owing to a  $Ca^{2+}$  re uphill transmembrane solute transport (Arias, 1989; creation cluminal and Awasthi, 1993). ATP splitting activity in the canaliculus and bile ducts is owing to a  $Ca^{2+}$  requiring  $Mg^{2+}$ -stimulated ATPase, which is most Zimniak and Awasthi, 1993). ATP splitting activity<br>the canaliculus and bile ducts is owing to a  $Ca^{2+}$  requi<br>ing  $Mg^{2+}$ -stimulated ATPase, which is most likely mo<br>than one ATPase protein (Gautam et al., 1987). The<br>seem ing  $Mg^{2+}$ -stimulated ATPase, which is most likely more<br>than one ATPase protein (Gautam et al., 1987). There relative to the enlarged bile acid pool in diabetic rodents.<br>seem to be at least four transporting ATPases in ing  $Mg^{2+}$ -stimulated ATPase, which is most likely mothan one ATPase protein (Gautam et al., 1987). The seem to be at least four transporting ATPases in canaticular membranes, identified as the P-glycoprotein, biacid ca than one ATPase protein (Gautam et al., 1987). There seem to be at least four transporting ATPases in canalicular membranes, identified as the P-glycoprotein, bile acid carrier, and the non-bile acid organic anion transpor seem to be at least four transporting ATPases in canal-<br>icular membranes, identified as the P-glycoprotein, bile<br>acid carrier, and the non-bile acid organic anion trans-<br>porter (Arias et al. 1993; Zimniak and Awasthi, 1993 icular membranes, identified as the P-glycoprotein, bilacid carrier, and the non-bile acid organic anion transporter (Arias et al. 1993; Zimniak and Awasthi, 1993)<br>P-Glycoproteins, products of the multiple resistance<br>genes acid carrier, and the non-bile acid organic anion trans-<br>porter (Arias et al. 1993; Zimniak and Awasthi, 1993).<br>P-Glycoproteins, products of the multiple resistance<br>genes, transport mostly hydrophobic, neutral, or posi-<br>ti porter (Arias et al. 1993; Zimniak and Awasthi, 1993;<br>P-Glycoproteins, products of the multiple resistan<br>genes, transport mostly hydrophobic, neutral, or pos<br>tively charged chemicals into bile (Arias, 1990; Endico<br>and Ling P-Glycoproteins, products of the multiple resist:<br>genes, transport mostly hydrophobic, neutral, or j<br>tively charged chemicals into bile (Arias, 1990; End<br>and Ling, 1989; Kamimoto et al., 1989). Bile acid tr<br>port can occur genes, transport mostly hydrophobic, neutral, or pos<br>tively charged chemicals into bile (Arias, 1990; Endicot<br>and Ling, 1989; Kamimoto et al., 1989). Bile acid trans<br>port can occur via a membrane potential dependen<br>carrier tively charged chemicals into bile (Arias, 1990; Endicott and Ling, 1989; Kamimoto et al., 1989). Bile acid transport can occur via a membrane potential dependent-carrier or the ATP-dependent bile acid transporter (Adachi port can occur via a membrane potential dependent-<br>carrier or the ATP-dependent bile acid transporter (Ada-<br>chi et al., 1991; Arias et al., 1993; Nishida et al., 1991;<br>Ruetz et al., 1987; Zimniak and Awasthi, 1993). Finall port can occur via a membrane potential dependent-<br>carrier or the ATP-dependent bile acid transporter (Ada-<br>chi et al., 1991; Arias et al., 1993; Nishida et al., 1991;<br>Ruetz et al., 1987; Zimniak and Awasthi, 1993). Finall carrier or the ATP-dependent bile acid transporter (Ada<br>chi et al., 1991; Arias et al., 1993; Nishida et al., 1991<br>Ruetz et al., 1987; Zimniak and Awasthi, 1993). Finally<br>the nonbile acid carrier can move organic anions ac chi et al., 1991; Arias et al., 1993; Nishida et al., 1991;<br>Ruetz et al., 1987; Zimniak and Awasthi, 1993). Finally,<br>the nonbile acid carrier can move organic anions across<br>the membrane via either an electrogenic or an ATP Ruetz et al., 1987; Zimniak and Awasthi, 1993). Finally,<br>the nonbile acid carrier can move organic anions across<br>the membrane via either an electrogenic or an ATP-<br>dependent process (Ishikawa et al., 1990; Nishida et al.,<br> the nonbile acid carrier can move organic anions across grathe membrane via either an electrogenic or an ATP-<br>dependent process (Ishikawa et al., 1990; Nishida et al., car<br>1992). The multispecific organic anion transporter the membrane via either an electrogenic or an ATP-<br>dependent process (Ishikawa et al., 1990; Nishida et al.,<br>1992). The multispecific organic anion transporter me-<br>diates transport of bilirubin diglucuronide, sulfated and<br> dependent process (Ishikawa et al., 1990; Nishida et al., 1992). The multispecific organic anion transporter mediates transport of bilirubin diglucuronide, sulfated and glucuronidated bile salts, cysteinyl leukotrienes and 1992). The multispecific organic anion transporter mediates transport of bilirubin diglucuronide, sulfated and Succuronidated bile salts, cysteinyl leukotrienes and glutathione S-conjugates (Kitamura et al., 1990; Kobayas diates transport of bilirubin diglucuronide, sulfated and Sieplucuronidated bile salts, cysteinyl leukotrienes and glu-<br>tathione S-conjugates (Kitamura et al., 1990; Kobayashi glu<br>et al., 1990; Kuipers et al., 1988, 1989). glucuronidated bile salts, cysteinyl leukotrienes and glu-<br>tathione S-conjugates (Kitamura et al., 1990; Kobayashi glu<br>et al., 1990; Kuipers et al., 1988, 1989). Recent evidence tra<br>in canalicular vesicles indicates that t tathione S-conjugates (Kitamura et al., 1990; Kobayashi<br>et al., 1990; Kuipers et al., 1988, 1989). Recent evidence<br>in canalicular vesicles indicates that the canalicular bile<br>acid carrier exhibits a broad substrate specifi al., 1990). canalicular vesicles indicates that the canalicular bile<br>id carrier exhibits a broad substrate specificity and<br>transports other monovalent organic anions (Tamai et<br>, 1990).<br>Secondary canalicular transport systems use ion g acid carrier exhibits a broad substrate specificity and cotransports other monovalent organic anions (Tamai e al., 1990).<br>Secondary canalicular transport systems use ion gradients coupling substrate transport to parallel o

cotransports other monovalent organic anions (Tamai<br>al., 1990).<br>Secondary canalicular transport systems use ion gr<br>dients coupling substrate transport to parallel or an<br>parallel ion fluxes or to electrochemical potential d dients coupling substrate transport to parallel or anti-<br>parallel ion fluxes or to electrochemical potential differ-<br>ences across the canalicular membrane. A chloride-<br>driven chloride-bicarbonate exchange system (Meier, Secondary canalicular transport systems use ion gra-<br>dients coupling substrate transport to parallel or anti-<br>parallel ion fluxes or to electrochemical potential differ-<br>ences across the canalicular membrane. A chloride-<br> dients coupling substrate transport to parallel or anti-<br>parallel ion fluxes or to electrochemical potential differ-<br>ences across the canalicular membrane. A chloride-<br>sightiven chloride-bicarbonate exchange system (Meier parallel ion fluxes or to electrochemical potential diffences across the canalicular membrane. A chloridriven chloride-bicarbonate exchange system (Me 1988) leads to osmotically active  $HCO_3^-$  within canaliculus. The  $HCO_$ ences across the canalicular membrane. A chloridity driven chloride-bicarbonate exchange system (Mei<br>1988) leads to osmotically active  $HCO_3^-$  within to<br>canaliculus. The  $HCO_3^-/Cl^-$ -exchanger in the canaliculus acts in syn driven chloride-bicarbonate exchange system (Meier, 1988) leads to osmotically active  $HCO_3^-$  within the (canaliculus. The  $HCO_3^-/Cl^-$ -exchanger in the canaliculus acts in synergy with basolateral sodium-dependent to proto canaliculus. The  $HCO_3^-/Cl^-$ -exchanger in the canaliculus acts in synergy with basolateral sodium-dependent proton extrusion by a  $Na^+/H^+$ -antiport (Rothstein, 1989) and sodium-dependent bicarbonate uptake by Na<sup>+</sup>- $HCO_3^$ canaliculus. The  $HCO_3^-/Cl^-$ -exchanger in the canal<br>lus acts in synergy with basolateral sodium-depend<br>proton extrusion by a Na<sup>+</sup>/H<sup>+</sup>-antiport (Rothstein, 19<br>and sodium-dependent bicarbonate uptake by N<br> $HCO_3^-$ -cotranspo s acts in synergy with basolateral sodium-dependent troton extrusion by a  $Na^+/H^+$ -antiport (Rothstein, 1989) and sodium-dependent bicarbonate uptake by  $Na^+$ - cr<br> $CO_3^-$ -cotransport (Weintraub and Macken, 1989). 197he mec  $HCO<sub>3</sub>$ <sup>-</sup>-cotransport (Weintraub and Macken, 1989).

and sodium-dependent bicarbonate uptake by Na<sup>+</sup>- $HCO_3$ <sup>-</sup>-cotransport (Weintraub and Macken, 1989).<br>The mechanisms of bile acid traffic into and out of hepatocytes have been reviewed recently (Meier, 1989, 1991). Canalic

canalicular bile secretion (Arias et al., 1993; Meier, tion. The second mechanism is an ATP-dependent pri-<br>1988, 1989). Primary transport systems utilize the mary active organic anion pump for dianionic bile acid<br>chemical EPATOBILIARY FUNCTION 13<br>sents the rate limiting step in overall hepatobiliary se-<br>cretion of bile acids and is a concentrative transport EPATOBILIARY FUNCTION 13<br>sents the rate limiting step in overall hepatobiliary se-<br>cretion of bile acids and is a concentrative transport<br>process that occurs against an unfavorable bile-to-cell EPATOBILIARY FUNCTION 13<br>sents the rate limiting step in overall hepatobiliary se-<br>cretion of bile acids and is a concentrative transport<br>process that occurs against an unfavorable bile-to-cell<br>concentration gradient of at sents the rate limiting step in overall hepatobiliary secretion of bile acids and is a concentrative transport process that occurs against an unfavorable bile-to-cell concentration gradient of at least 10:1. Two separate t sents the rate limiting step in overall hepatobiliary secretion of bile acids and is a concentrative transport process that occurs against an unfavorable bile-to-cell concentration gradient of at least 10:1. Two separate t cretion of bile acids and is a concentrative transport process that occurs against an unfavorable bile-to-concentration gradient of at least 10:1. Two separatransport mechanisms have been identified and potentially charact process that occurs against an unfavorable bile-to-c<br>concentration gradient of at least 10:1. Two separatransport mechanisms have been identified and patially characterized. One is a saturable, electrical pote<br>tial-driven concentration gradient of at least 10:1. Two separat<br>transport mechanisms have been identified and partially characterized. One is a saturable, electrical poten<br>tial-driven pathway for monoanionic, relatively hydro<br>philic transport mechanisms have been identified and partially characterized. One is a saturable, electrical potential-driven pathway for monoanionic, relatively hydrophilic bile acid amidates and taurocholate that is  $Na^+$ -inde tially characterized. One is a saturable, electrical potential-driven pathway for monoanionic, relatively hydrophilic bile acid amidates and taurocholate that is  $Na^+$ -independent (Meier et al., 1984, 1987) where the intr tial-driven pathway for monoanionic, relatively hydrephilic bile acid amidates and taurocholate that is Na independent (Meier et al., 1984, 1987) where the intracellular negative electrical potential (-30 to 40 m) represen philic bile acid amidates and taurocholate that is Na<sup>+</sup>-independent (Meier et al., 1984, 1987) where the intracellular negative electrical potential (-30 to 40 mV) represents an important driving force for bile acid secre independent (Meier et al., 1984, 1987) where the<br>intracellular negative electrical potential  $(-30 \text{ to } 40 \text{ mV})$ <br>represents an important driving force for bile acid secre-<br>tion. The second mechanism is an ATP-dependent pr intracellular negative electrical potential (-30 to 40 mV)<br>represents an important driving force for bile acid secre-<br>tion. The second mechanism is an ATP-dependent pri-<br>mary active organic anion pump for dianionic bile ac represents an important driving force for bile acid secretion. The second mechanism is an ATP-dependent primary active organic anion pump for dianionic bile acid 3–0-glucuronides and bile acid sulfates. In addition, microt tion. The second mechanism is an ATP-dependent<br>mary active organic anion pump for dianionic bile<br>3–0-glucuronides and bile acid sulfates. In addition<br>crotubule-dependent vesicle-mediated exceytosis se<br>to play an increasing mary active organic anion pump for dianionic bile acid 3–0-glucuronides and bile acid sulfates. In addition, microtubule-dependent vesicle-mediated exocytosis seems<br>to play an increasing role in the presence of supraphysio 3–0-glucuronides and bile acid sulfates. In addition, microtubule-dependent vesicle-mediated exocytosis seems<br>to play an increasing role in the presence of supraphysi-<br>ological bile acid loads (Meier, 1991). No one has yet crotubule-dependent vesicle-mediated exocytosis seems<br>to play an increasing role in the presence of supraphysi-<br>ological bile acid loads (Meier, 1991). No one has yet<br>determined how important this exocytosis mechanism is<br>r determined how important this exocytosis mechanism is

crotubule-dependent veside-mediated exccytosis seems<br>to play an increasing role in the presence of supraphysiological bile acid loads (Meier, 1991). No one has yet<br>determined how important this exccytosis mechanism is<br>rel determined how important this exocytosis mechanism is<br>relative to the enlarged bile acid pool in diabetic rodents.<br>The canalicular bile acid carrier is very likely a 100 to<br>110 kD protein (Fricker et al., 1987; Hong and Do relative to the enlarged bile acid pool in diabetic rodents.<br>The canalicular bile acid carrier is very likely a 100 to<br>110 kD protein (Fricker et al., 1987; Hong and Doyle,<br>1987; Kramer and Schneider, 1989; Ruetz et al., 1 The canalicular bile acid carrier is very likely a 100 to<br>
110 kD protein (Fricker et al., 1987; Hong and Doyle,<br>
1987; Kramer and Schneider, 1989; Ruetz et al., 1987).<br>
Polyclonal antibodies raised against this protein i 110 kD protein (Fricker et al., 1987; Hong and Doyle, 1987; Kramer and Schneider, 1989; Ruetz et al., 1987).<br>Polyclonal antibodies raised against this protein inhibit both taurocholate uptake into as well as efflux from ca 1987; Kramer and Schneider, 1989; Ruetz et al., 1987).<br>Polyclonal antibodies raised against this protein inhibit<br>both taurocholate uptake into as well as efflux from<br>canalicular vesicles (Ruetz et al., 1987; Sippel et al., both taurocholate uptake into as well as efflux from canalicular vesicles (Ruetz et al., 1987; Sippel et al., 1990). However, the identity of the bile acid transporting protein is unclear, as other polypeptides with simila both taurocholate uptake into as well as efflux from canalicular vesicles (Ruetz et al., 1987; Sippel et al. 1990). However, the identity of the bile acid transportin protein is unclear, as other polypeptides with simila m canalicular vesicles (Ruetz et al., 1987; Sippel et al., 1990). However, the identity of the bile acid transporting protein is unclear, as other polypeptides with similar molecular weights are present at the canalicular me 1990). However, the identity of the bile acid transporting<br>protein is unclear, as other polypeptides with similar<br>molecular weights are present at the canalicular mem-<br>brane (Margollis et al., 1990; McCaughan et al., 1990 protein is unclear, as other polypeptides with simila<br>molecular weights are present at the canalicular men<br>brane (Margollis et al., 1990; McCaughan et al., 1990<br>The carrier-mediated secretion is believed to occur l<br>facilit gradient. ane (Margollis et al., 1990; McCaughan et al., 1990).<br>he carrier-mediated secretion is believed to occur by<br>cilitated diffusion down the bile acid electrochemical<br>adient.<br>There also seems to be an interrelated complex for

The carrier-mediated secretion is believed to occurrier-mediated diffusion down the bile acid electrocher gradient.<br>There also seems to be an interrelated complex for carrier-mediated excretion of glutathione, glutathionin facilitated diffusion down the bile acid electrochemical<br>gradient.<br>There also seems to be an interrelated complex for the<br>carrier-mediated excretion of glutathione, glutathione-<br>conjugates, and oxidized glutathione (Lauter gradient.<br>There also seems to be an interrelated complex for the<br>carrier-mediated excretion of glutathione, glutathione-<br>conjugates, and oxidized glutathione (Lauterburg, 1991;<br>Sies, 1989) with sodium-dependent reflux of g There also seems to be an interrelated complex for the carrier-mediated excretion of glutathione, glutathione-conjugates, and oxidized glutathione (Lauterburg, 1991; Sies, 1989) with sodium-dependent reflux of glutamate a carrier-mediated excretion of glutathione, glutathio<br>conjugates, and oxidized glutathione (Lauterburg, 19<br>Sies, 1989) with sodium-dependent reflux of glutam<br>and glycine (Ballatori et al., 1986). The secreted redu<br>glutathi conjugates, and oxidized glutathione (Lauterburg, 1991;<br>Sies, 1989) with sodium-dependent reflux of glutamate<br>and glycine (Ballatori et al., 1986). The secreted reduced<br>glutathione molecule is processed by  $\gamma$ -glutamyl-<br> Sies, 1989) with sodium-dependent reflux of glutamate<br>and glycine (Ballatori et al., 1986). The secreted reduced<br>glutathione molecule is processed by  $\gamma$ -glutamyl-<br>transpeptidase, thereby producing glutamate and the<br>dipe and glycine (Ballatori et al., 1986). The secreted reduced glutathione molecule is processed by  $\gamma$ -glutamyl-<br>transpeptidase, thereby producing glutamate and the dipeptide cysteine-glycine. Glutamate is reabsorbed by a<br>s glutathione molecule is processed by  $\gamma$ -glutamyl-<br>transpeptidase, thereby producing glutamate and the<br>dipeptide cysteine-glycine. Glutamate is reabsorbed by a<br>sodium-driven carrier from the lumen back into the cell<br>(Bal transpeptidase, thereby producing glutamate and the dipeptide cysteine-glycine. Glutamate is reabsorbed b sodium-driven carrier from the lumen back into the conditional dipeptide cysteine/glyc might escape or be split furt dipeptide cysteine-glycine. Glutamate is reabsorbed by a sodium-driven carrier from the lumen back into the cell (Ballatori et al., 1986). The dipeptide cysteine/glycine might escape or be split further by luminal dipeptid sodium-driven carrier from the lumen back into the cell<br>(Ballatori et al., 1986). The dipeptide cysteine/glycine<br>might escape or be split further by luminal dipepti-<br>dylpeptidase IV. Glycine and cysteine also undergo re-<br>a (Ballatori et al., 1986). The dipeptide cysteine/glycine<br>might escape or be split further by luminal dipepti-<br>dylpeptidase IV. Glycine and cysteine also undergo re-<br>absorptive pathways. In contrast, oxidized glutathione<br>a might escape or be split further by luminal dipepti-<br>dylpeptidase IV. Glycine and cysteine also undergo re-<br>absorptive pathways. In contrast, oxidized glutathione<br>and glutathione-drug conjugates do not seem to be split<br>sig dylpeptidase IV. Glycine and cysteine also undergo<br>absorptive pathways. In contrast, oxidized glutathion<br>and glutathione-drug conjugates do not seem to be sp<br>significantly by biliary  $\gamma$ -glutamyltranspeptidase. A n<br>ural absorptive pathways. In contrast, oxidized gluta<br>and glutathione-drug conjugates do not seem to b<br>significantly by biliary  $\gamma$ -glutamyltranspeptidase.<br>ural glutathione conjugate, leukotriene-gluta<br>(leukotriene C<sub>4</sub>), is and glutathione-drug conjugates do not seem to be<br>significantly by biliary  $\gamma$ -glutamyltranspeptidase.<br>ural glutathione conjugate, leukotriene-glutat<br>(leukotriene C<sub>4</sub>), is split by  $\gamma$ -glutamyltranspept<br>starting the ca significantly by biliary  $\gamma$ -glutamyltranspeptidase. A natural glutathione conjugate, leukotriene-glutathione (leukotriene C<sub>4</sub>), is split by  $\gamma$ -glutamyltranspeptidase, starting the catabolic cascade of the cysteinyl-l ural glutathione conjugate, leukotriene-glutathione<br>(leukotriene  $C_4$ ), is split by  $\gamma$ -glutamyltranspeptidase,<br>starting the catabolic cascade of the cysteinyl-leuko-<br>trienes leukotriene  $C_4$ , leukotriene  $D_4$ , leukot (leukotriene  $C_4$ ), is split by  $\gamma$ -glutamyltranspeptidase,<br>starting the catabolic cascade of the cysteinyl-leuko-<br>trienes leukotriene  $C_4$ , leukotriene  $D_4$ , leukotriene  $E_4$ ,<br>and leukotriene-N-acetyl- $E_4$ . Leukotr starting the catabolic cascade of the cysteinyl-leuko-<br>trienes leukotriene  $C_4$ , leukotriene  $D_4$ , leukotriene  $E_4$ ,<br>and leukotriene-N-acetyl- $E_4$ . Leukotrienes are also se-<br>creted by putative protein carriers into bi and leukotriene-N-acetyl-E<sub>4</sub>. Leukotrienes are also se-<br>creted by putative protein carriers into bile (Huber et al.,<br>1989; Lauterburg, 1991). This transport system is<br>closely related to or identical with the bilirubin-di and leukotriene-N-acetyl-E<sub>4</sub>. Leukotrienes are also a creted by putative protein carriers into bile (Huber et a 1989; Lauterburg, 1991). This transport system closely related to or identical with the bilirubin-digluo ron creted by putative protein carriers into bile (Huber et al., 1989; Lauterburg, 1991). This transport system is closely related to or identical with the bilirubin-diglucuronide transporter of hepatocytes, because both bilir

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14 waTKINS AN<br>mutant rats (Huber et al., 1987). It is as yet unclear<br>whether endotoxins directly affect transport and WATKINS AND SA<br>mutant rats (Huber et al., 1987). It is as yet unclear wit<br>whether endotoxins directly affect transport and con<br>whether basolateral uptake or canalicular secretion of are waTKINS AND S<br>mutant rats (Huber et al., 1987). It is as yet unclear with<br>ether endotoxins directly affect transport and complete<br>whether basolateral uptake or canalicular secretion of an<br>leukotrienes might be involved in mutant rats (Huber et al., 1987). It is as yet uncleused whether endotoxins directly affect transport at whether basolateral uptake or canalicular secretion leukotrienes might be involved in endotoxin action. In addition t utant rats (Huber et al., 1987). It is as yet unclear<br>nether endotoxins directly affect transport and<br>nether basolateral uptake or canalicular secretion of<br>akotrienes might be involved in endotoxin action.<br>In addition to t

whether endotoxins directly affect transport and<br>whether basolateral uptake or canalicular secretion of<br>leukotrienes might be involved in endotoxin action.<br>In addition to the multi-drug resistance Gp170 carrier<br>protein, th whether basolateral uptake or canalicular secretion of all eukotrienes might be involved in endotoxin action. polynomially in addition to the multi-drug resistance Gp170 carrier in protein, the canalicular membrane possess leukotrienes might be involved in endotoxin action.<br>In addition to the multi-drug resistance Gp170 carrier<br>protein, the canalicular membrane possesses at least<br>two cation carriers for transporting type I and type II<br>compou In addition to the multi-drug resistance Gp170 carrie<br>protein, the canalicular membrane possesses at leat<br>two cation carriers for transporting type I and type<br>compounds (Steen and Meijer, 1991). Photoaffinity la<br>beling wit protein, the canalicular membrane possesses at least wive cation carriers for transporting type I and type II as<br>compounds (Steen and Meijer, 1991). Photoaffinity labeling with a type I organic cation uncovers two mem-<br>br two cation carriers for transporting type I and type II<br>compounds (Steen and Meijer, 1991). Photoaffinity la-<br>beling with a type I organic cation uncovers two mem-<br>brane polypeptides with apparent molecular weights of<br>48 k beling with a type I organic cation uncovers two membrane polypeptides with apparent molecular weights of 48 kD and 72 kD (Steen and Meijer, 1991). Photoaffinity labeling of isolated cells with a photolabile bulky mono-val brane polypeptides with apparent molecular weights of biased 48 kD and 72 kD (Steen and Meijer, 1991). Photoaffinity dabeling of isolated cells with a photolabile bulky monovalent quaternary amine that was used as a type 48 kD and 72 kD (Steen and Meijer, 1991). Photoaffinity dent of labeling of isolated cells with a photolabile bulky mono-<br>valent quaternary amine that was used as a type II ids, choose model compound reveals two plasma me labeling of isolated cells with a photolabile bulky movelent quaternary amine that was used as a type model compound reveals two plasma membrane bindipolypeptides with apparent molecular weights of 48 and 50 kD. Further wo valent quaternary amine that was use<br>model compound reveals two plasma mer<br>polypeptides with apparent molecular wo<br>and 50 kD. Further work to isolate, pur<br>terize these putative carriers is needed. terize these putative carriers is needed.

Profound alterations in bile composition are observed<br>in insulin-deficient diabetic patients or experimental an-<br>imals. Very early studies indicate that diabetic patients<br> $\frac{1}{2}$  and an-linear triglycerides, as well as a B. Diabetes-induced Alterations of the Biliary Excretion<br>of Endogenous Compounds<br>Profound alterations in bile composition are observed<br>in insulin-deficient diabetic patients or experimental an-<br>imals. Very early studies in imals. Diabetes-induced Atterations of the Bittary Excretion<br>of Endogenous Compounds<br>Profound alterations in bile composition are observed<br>in insulin-deficient diabetic patients or experimental an-<br>imals. Very early studie at autopsy have a greater incidence of gallstones than insulin-deficient diabetic patients or experimental animals. Very early studies indicate that diabetic patients at autopsy have a greater incidence of gallstones than Profound alterations in bile composition are observed<br>in insulin-deficient diabetic patients or experimental an-<br>imals. Very early studies indicate that diabetic patients<br>at autopsy have a greater incidence of gallstones t in insulin-deficient diabetic patients or experimental animals. Very early studies indicate that diabetic patients<br>at autopsy have a greater incidence of gallstones than<br>nondiabetics (Goldstein and Schein, 1963; Lieber, 19 imals. Very early studies indicate that diabetic patients<br>at autopsy have a greater incidence of gallstones than<br>nondiabetics (Goldstein and Schein, 1963; Lieber, 1952).<br>A large study with 775 diabetic patients versus 1308 at autopsy have a greater incidence of gallstones than<br>nondiabetics (Goldstein and Schein, 1963; Lieber, 1952).<br>A large study with 775 diabetic patients versus 1308<br>nondiabetic patients failed to determine a positive cor-<br> nondiabetics (Goldstein and Schein, 1963; Lieber, 1952).<br>A large study with 775 diabetic patients versus 1308<br>nondiabetic patients failed to determine a positive cor-<br>relation between diabetes and cholelithiasis (Honore,<br>1 nondiabetic patients failed to determine a positive correlation between diabetes and cholelithiasis (Honore, 1980). In contrast, there is epidemiological evidence that diabetics are two to three times more likely than nond nondiabetic patients failed to determine a positive correlation between diabetes and cholelithiasis (Honore, 1980). In contrast, there is epidemiological evidence that diabetics are two to three times more likely than nond relation between diabetes and cholelithiasis (Honore, 1980). In contrast, there is epidemiological evidence that diabetics are two to three times more likely than nondiabetic patients to have gallbladder disease (Strom et 1980). In contrast, there is epidemiological evidence that<br>
diabetics are two to three times more likely than nondi-<br>
abetic patients to have gallbladder disease (Strom et al.,<br>
1986). Unfortunately, other work finds that diabetics are two to three times more likely than nondiabetic patients to have gallbladder disease (Strom et al., 1986). Unfortunately, other work finds that in type II diabetic patients cholelithiasis is associated with abetic patients to have gallbladder disease (Strom et al., 1986). Unfortunately, other work finds that in type II diabetic patients cholelithiasis is associated with obesity and not diabetes (Haber and Heaton, 1979), and d diabetic patients cholelithiasis is associated with obesity<br>and not diabetes (Haber and Heaton, 1979), and dietary<br>ascorbic acid deficiency, which exacerbates cholesterol<br>gallstone formation and increases risk for cholelit diabetic patients cholelithiasis is associated with obesi<br>and not diabetes (Haber and Heaton, 1979), and dieta<br>ascorbic acid deficiency, which exacerbates cholester<br>gallstone formation and increases risk for cholelithias<br>i and not diabetes (Haber and Heaton, 1979), and dietary<br>ascorbic acid deficiency, which exacerbates cholesterol<br>gallstone formation and increases risk for cholelithiasis<br>in diabetics, could also be involved (Simon, 1993). ascorbic acid deficiency, which exacerbates cholesterol gallstone formation and increases risk for cholelithiasis in diabetics, could also be involved (Simon, 1993). Lithogenesis may also result from some metabolic defect gallstone formation and increases risk for cholelithiasis<br>in diabetics, could also be involved (Simon, 1993). Litho-<br>genesis may also result from some metabolic defect in<br>the liver relating to excessive synthesis and excre in diabetics, could also be involved (Simon, 1993). Lit<br>genesis may also result from some metabolic defect<br>the liver relating to excessive synthesis and excretior<br>cholesterol, a change in bile acids, or both (Bouchi<br>1980; genesis may also result from some metabolic defect in the liver relating to excessive synthesis and excretion of the cholesterol, a change in bile acids, or both (Bouchier, ball 1980; Key et al., 1980; Saudek and Eder, 197 the liver relating to excessive synthesis and excretion of cholesterol, a change in bile acids, or both (Bouchier, 1980; Key et al., 1980; Saudek and Eder, 1979). Insulintreated diabetic patients have increased excretion o cholesterol, a change in bile acids, or both (Bouchier, <sup>Da</sup><br>1980; Key et al., 1980; Saudek and Eder, 1979). Insulin-<br>treated diabetic patients have increased excretion of bile<br>and bile acids (Molloy and Tomkin, 1978), whe 1980; Key et al., 1980; Saudek and Eder, 1979). Insu<br>treated diabetic patients have increased excretion of<br>and bile acids (Molloy and Tomkin, 1978), whereas<br>treated people with diabetes show even higher fecal<br>acid excretio treated diabetic patients have increased excretion of bile<br>and bile acids (Molloy and Tomkin, 1978), whereas un-<br>treated people with diabetes show even higher fecal bile<br>acid excretion (Bennion and Grundy, 1977). Non-insuand bile acids (Molloy and Tomkin, 1978), whereas untreated people with diabetes show even higher fecal bile acid excretion (Bennion and Grundy, 1977). Non-insulin-dependent people with diabetes seem to excrete increased l treated people with diabetes show even higher fecal bile<br>acid excretion (Bennion and Grundy, 1977). Non-insu-<br>lin-dependent people with diabetes seem to excrete in-<br>creased levels of 12-ketolithocholic acid and cholesterol acid excretion (Bennion and Grundy, 1977). Non-insu-<br>lin-dependent people with diabetes seem to excrete in-<br>creased levels of 12-ketolithocholic acid and cholesterol<br>but decreased levels of cholic acid and deoxycholic acid lin-dependent people with diabetes seem to excrete<br>creased levels of 12-ketolithocholic acid and choleste<br>but decreased levels of cholic acid and deoxycholic a<br>(Andersen et al., 1987). Other studies, using differ<br>patient b creased levels of 12-ketolithocholic acid and cholesterol<br>but decreased levels of cholic acid and deoxycholic acid<br>(Andersen et al., 1987). Other studies, using different<br>patient bases, indicate that the bile of insulin-de but decreased levels of cholic acid and deoxycholic acid (Andersen et al., 1987). Other studies, using different patient bases, indicate that the bile of insulin-dependent people with diabetes is nearly normal in compositi (Andersen et al., 1987). Other studies, using different patient bases, indicate that the bile of insulin-dependent people with diabetes is nearly normal in composition (Andersen et al., 1986, 1988; Ponz de Leon et al., 197 patient bases, indicate that the bile of insulin-dependent<br>people with diabetes is nearly normal in composition<br>(Andersen et al., 1986, 1988; Ponz de Leon et al., 1978).<br>Meinders and coworkers (1981) postulate that lower i (Andersen et al., 1986, 1988; Ponz de Leon et al., 1978). with cholate (Simon et al., 1982) is manifested as an Meinders and coworkers (1981) postulate that lower in-<br>testinal motility, and therefore greater bacterial act Meinders and coworkers (1981) postulate that lower in-

) SANDERS<br>with diabetes. Larger epidemiological studies, which<br>control for obesity and hyperlipoproteinemic disorders, COM SANDERS<br>with diabetes. Larger epidemiological studies, which<br>control for obesity and hyperlipoproteinemic disorders,<br>are needed to determine whether or not diabetes predis-AMDERS<br>with diabetes. Larger epidemiological studies, whicontrol for obesity and hyperlipoproteinemic disorde<br>are needed to determine whether or not diabetes pred<br>poses patients to cholelithiasis. Most of the availal with diabetes. Larger epidemiological studies, which<br>control for obesity and hyperlipoproteinemic disorders,<br>are needed to determine whether or not diabetes predis-<br>poses patients to cholelithiasis. Most of the available<br>i control for obesity and hyperlipoproteinemic disorders,<br>are needed to determine whether or not diabetes predis-<br>poses patients to cholelithiasis. Most of the available<br>information suggests that the risk of treatment out-<br>w control for obesity and hyperlipoproteinemic disorders,<br>are needed to determine whether or not diabetes predis-<br>poses patients to cholelithiasis. Most of the available<br>information suggests that the risk of treatment out-<br>w are needed to determine whether or not diabetes p<br>poses patients to cholelithiasis. Most of the ava<br>information suggests that the risk of treatmen<br>weighs the potential benefits in most patients<br>asymptomatic gallstones (Har ses patients to cholelithiasis. Most of the available<br>formation suggests that the risk of treatment out-<br>eighs the potential benefits in most patients with<br>ymptomatic gallstones (Hartford et al., 1990).<br>Rahman and Coleman

beling with a type I organic cation uncovers two mem-<br>perfused rat liver that at high bile-acid secretion rates,<br>brane polypeptides with apparent molecular weights of<br>biliary cholesterol and phospholipid secretion is depe and 50 kD. Further work to isolate, purify and charac-<br>
terize these putative carriers is needed.<br>
al., 1990a; Watkins and Dykstra, 1987; Wey et al., 1984).<br>
Serum and liver triacylglycerol concentrations are also<br> *B. Dia* information suggests that the risk of treatment out-<br>weighs the potential benefits in most patients with<br>asymptomatic gallstones (Hartford et al., 1990).<br>Rahman and Coleman (1986) have shown in isolated<br>perfused rat liver weighs the potential benefits in most patients will assumptomatic gallstones (Hartford et al., 1990).<br>Rahman and Coleman (1986) have shown in isolat<br>perfused rat liver that at high bile-acid secretion rat<br>biliary cholester asymptomatic gallstones (Hartford et al., 1990).<br>Rahman and Coleman (1986) have shown in isola<br>perfused rat liver that at high bile-acid secretion rat<br>biliary cholesterol and phospholipid secretion is dep<br>dent on that of b Rahman and Coleman (1986) have shown in isolated<br>perfused rat liver that at high bile-acid secretion rates,<br>biliary cholesterol and phospholipid secretion is depen-<br>dent on that of bile acids. In either alloxan- or strepto perfused rat liver that at high bile-acid secretion rates,<br>biliary cholesterol and phospholipid secretion is depen-<br>dent on that of bile acids. In either alloxan- or strepto-<br>zotocin-treated rats, the biliary concentration biliary cholesterol and phospholipid secretion is dependent on that of bile acids. In either alloxan- or strepto-<br>zotocin-treated rats, the biliary concentration of bile ac-<br>ids, cholesterol, lecithin and phospholipids is dent on that of bile acids. In either alloxan- or strepto-<br>zotocin-treated rats, the biliary concentration of bile ac-<br>ids, cholesterol, lecithin and phospholipids is markedly<br>increased (Carnovale et al., 1987; Hassan and zotocin-treated rats, the biliary concentration of bile ac-<br>ids, cholesterol, lecithin and phospholipids is markedly<br>increased (Carnovale et al., 1987; Hassan and Subbiah,<br>1980; Kirkpatrick and Kraft, 1984; Nervi et al., 1 ids, cholesterol, lecithin and phospholipids is markedly<br>increased (Carnovale et al., 1987; Hassan and Subbiah,<br>1980; Kirkpatrick and Kraft, 1984; Nervi et al., 1974,<br>1978; Siow et al., 1991; Stohs et al., 1979; Villanueva increased (Carnovale et al., 1987; Hassan and Subbiah,<br>1980; Kirkpatrick and Kraft, 1984; Nervi et al., 1974,<br>1978; Siow et al., 1991; Stohs et al., 1979; Villanueva et<br>al., 1990a; Watkins and Dykstra, 1987; Wey et al., 19 1980; Kirkpatrick and Kraft, 1984; Nervi et al., 1974,<br>1978; Siow et al., 1991; Stohs et al., 1979; Villanueva et<br>al., 1990a; Watkins and Dykstra, 1987; Wey et al., 1984).<br>Serum and liver triacylglycerol concentrations are 1978; Siow et al., 1991; Stohs et al., 1979; Villanueva et al., 1990a; Watkins and Dykstra, 1987; Wey et al., 1984).<br>Serum and liver triacylglycerol concentrations are also<br>elevated (Woods et al., 1981). Akiyoshi and cowor al., 1990a; Watkins and Dykstra, 1987; Wey et al., 1984).<br>Serum and liver triacylglycerol concentrations are also<br>elevated (Woods et al., 1981). Akiyoshi and coworkers<br>(1986) note that gallstones produced by genetic diabet Serum and liver triacylglycerol concentrations are also<br>elevated (Woods et al., 1981). Akiyoshi and coworkers<br>(1986) note that gallstones produced by genetic diabetic<br>mice have cholesterol as a major (greater than 85%)<br>com elevated (Woods et al., 1981). Akiyoshi and coworkers (1986) note that gallstones produced by genetic diabetic mice have cholesterol as a major (greater than 85%) component. Alloxan-induced diabetic rabbits have reduced cl (1986) note that gallstones produced by genetic diabetic mice have cholesterol as a major (greater than 85%) component. Alloxan-induced diabetic rabbits have reduced clearance of plasma triglycerides, as well as altered a mice have cholesterol as a major (greater than 85%)<br>component. Alloxan-induced diabetic rabbits have re-<br>duced clearance of plasma triglycerides, as well as al-<br>tered apolipoprotein E expression and cholesterol ho-<br>meostas meostasis (Lenich et al., 1991). Other reports indicate that total bile acid secretion may not change (Hassan et al., 1982; Sadahiro et al., 1970), but the composition of duced clearance of plasma triglycerides, as well as altered apolipoprotein E expression and cholesterol homeostasis (Lenich et al., 1991). Other reports indicate that total bile acid secretion may not change (Hassan et al. tered apolipoprotein E expression and cholesterol h<br>meostasis (Lenich et al., 1991). Other reports indica<br>that total bile acid secretion may not change (Hassan<br>al., 1982; Sadahiro et al., 1970), but the composition<br>the bil meostasis (Lenich et al., 1991). Other reports indicate<br>that total bile acid secretion may not change (Hassan et<br>al., 1982; Sadahiro et al., 1970), but the composition of<br>the bile acid pool generally shows an increase in t that total bile acid secretion may not change (Hassan et al., 1982; Sadahiro et al., 1970), but the composition of the bile acid pool generally shows an increase in tauro-<br>chenodeoxycholate (Siow et al., 1991), a decrease al., 1982; Sadahiro et al., 1970), but the composition c<br>the bile acid pool generally shows an increase in taurc<br>chenodeoxycholate (Siow et al., 1991), a decrease in che<br>nodeoxycholate, and either no change or an increase the bile acid pool generally shows an increase in tauro-<br>chenodeoxycholate (Siow et al., 1991), a decrease in che-<br>nodeoxycholate, and either no change or an increase in<br>cholate (Hassan et al., 1982; Uchida et al., 1979). chenodeoxycholate (Siow et al., 1991), a decrease in chenodeoxycholate, and either no change or an increase in cholate (Hassan et al., 1982; Uchida et al., 1979). Hansson (1989) speculates that an increase in microsomal nodeoxycholate, and either no change or an increase in cholate (Hassan et al., 1982; Uchida et al., 1979). Hansson (1989) speculates that an increase in microsomal  $12\alpha$ -hydroxylase may explain the increased cholic acid sson (1989) speculates that an increase in microsomal  $12\alpha$ -hydroxylase may explain the increased cholic acid excretion into bile by diabetic rats. Illing (1981) suggests that alterations in bile acid output in streptozo  $12\alpha$ -hydroxylase may explain the increased cholic acid excretion into bile by diabetic rats. Illing (1981) suggests that alterations in bile acid output in streptozotocintreated rats may also result from a change in the  $12\alpha$ -hydroxylase may explain the increased cholic acid excretion into bile by diabetic rats. Illing (1981) suggests that alterations in bile acid output in streptozotocintreated rats may also result from a change in the excretion into bile by diabetic rats. Illing (1981) suggests<br>that alterations in bile acid output in streptozotocin-<br>treated rats may also result from a change in the en-<br>terohepatic circulation of bile acids, owing eithe treated rats may also result from a change in the enterohepatic circulation of bile acids, owing either to a direct effect of streptozotocin on the intestinal cells or to the antibiotic activity of streptozotocin on the in treated rats may also result from a change in the en-<br>terohepatic circulation of bile acids, owing either to a<br>direct effect of streptozotocin on the intestinal cells or to<br>the antibiotic activity of streptozotocin on the terohepatic circulation of bile acids, owing either to a<br>direct effect of streptozotocin on the intestinal cells or to<br>the antibiotic activity of streptozotocin on the intestinal<br>bacteria involved in bile acid biotransform direct effect of streptozotocin on the intestinal cells or to<br>the antibiotic activity of streptozotocin on the intestinal<br>bacteria involved in bile acid biotransformation. It is<br>also possible that the alterations noted in the antibiotic activity of streptozotocin on the intestinal<br>bacteria involved in bile acid biotransformation. It is<br>also possible that the alterations noted in bile acid<br>metabolism may be influenced by the hyperphagia, hybacteria involved in bile acid biotransformation. I<br>also possible that the alterations noted in bile a<br>metabolism may be influenced by the hyperphagia,<br>pertriglyceridemia, and hypercholesterolemia that<br>company the resultin also possible that the alterations noted in<br>metabolism may be influenced by the hyperpl<br>pertriglyceridemia, and hypercholesterolemia<br>company the resulting streptozotocin-induced<br>cemia (Wey et al., 1984; Young et al., 1982) etabolism may be influenced by the hyperphagia, hy-<br>rtriglyceridemia, and hypercholesterolemia that ac-<br>mpany the resulting streptozotocin-induced hypergly-<br>mia (Wey et al., 1984; Young et al., 1982).<br>Nevertheless, the var

pertriglyceridemia, and hypercholesterolemia that a company the resulting streptozotocin-induced hypergl cemia (Wey et al., 1984; Young et al., 1982).<br>Nevertheless, the variations in bile composition theocur in people with company the resulting streptozotocin-induced hypergly-<br>cemia (Wey et al., 1984; Young et al., 1982).<br>Nevertheless, the variations in bile composition that<br>occur in people with diabetes could affect biliary excre-<br>tory func cemia (Wey et al., 1984; Young et al., 1982).<br>Nevertheless, the variations in bile composition that<br>occur in people with diabetes could affect biliary excre-<br>tory function. In rats, adaptation to selective biliary<br>obstruct Nevertheless, the variations in bile composition that<br>occur in people with diabetes could affect biliary excre-<br>tory function. In rats, adaptation to selective biliary<br>obstruction and intraduodenal infusion of taurocholate occur in people with diabetes could affect biliary excretory function. In rats, adaptation to selective biliary obstruction and intraduodenal infusion of taurocholate (Adler et al., 1977), its repeated oral administration tory function. In rats, adaptation to selective biliary<br>obstruction and intraduodenal infusion of taurocholate<br>(Adler et al., 1977), its repeated oral administration<br>(Watkins and Klaassen, 1981), or repeated oral dosing<br>wi obstruction and intraduodenal infusion of taurocholate (Adler et al., 1977), its repeated oral administration (Watkins and Klaassen, 1981), or repeated oral dosing with cholate (Simon et al., 1982) is manifested as an incr (Adler et al., 1977), its repeated oral administration (Watkins and Klaassen, 1981), or repeated oral dosing with cholate (Simon et al., 1982) is manifested as an increase in bile acid excretory transport. Intravenous infu with cholate (Simon et al., 1982) is manifested as an infusion of taurocholate seems to be cholestatic and ei-

**a**spet

DIABETES MELLITUS AND HEPATOBILIARY FUNCTION <sup>15</sup>

DIABETES MELLITUS AND HET<br>(Carnovale et al., 1986; Villanueva et al., 1990a). Biliary thexeretion of proteins may also be stimulated by tauro-DIABETES MELLITUS A<br>(Carnovale et al., 1986; Villanueva et al., 1990a). Bilia<br>excretion of proteins may also be stimulated by tauro-<br>cholate injection (Marinelli et al., 1988). Taurolith DIABETES MELLITUS<br>(Carnovale et al., 1986; Villanueva et al., 1990a). Bi<br>excretion of proteins may also be stimulated by ta<br>cholate injection (Marinelli et al., 1988). Taurol<br>cholate infusion produces a rapid, transient ch (Carnovale et al., 1986; Villanueva et al., 1990a). Biliary<br>excretion of proteins may also be stimulated by tauro-<br>cholate injection (Marinelli et al., 1988). Taurolitho-<br>cholate infusion produces a rapid, transient choles (Carnovale et al., 1986; Villanueva et al., 1990a). Biliary<br>excretion of proteins may also be stimulated by tauro-<br>cholate injection (Marinelli et al., 1988). Taurolitho-<br>cholate infusion produces a rapid, transient choles excretion of proteins may also be stimulated by tauro-<br>cholate injection (Marinelli et al., 1988). Taurolitho-<br>cholate infusion produces a rapid, transient cholestasis<br>lev<br>and a decrease in hepatic cytochrome P450 content, cholate infusion produces a rapid, transient cholestasis and a decrease in hepatic cytochrome P450 content, perhaps owing to the effect of taurolithocholate on the function and composition of the smooth endoplasmic cholate infusion produces a rapid, transient cholestasis<br>and a decrease in hepatic cytochrome P450 content,<br>perhaps owing to the effect of taurolithocholate on the<br>function and composition of the smooth endoplasmic<br>reticul and a decrease in hepatic cytochrome P450 content, pre<br>perhaps owing to the effect of taurolithocholate on the creduction and composition of the smooth endoplasmic 198<br>reticulum (Berry et al., 1985). Another study indicat perhaps owing to the effect of taurolithocholate on the function and composition of the smooth endoplasmic reticulum (Berry et al., 1985). Another study indicates that insulin deficiency reduces bilirubin excretion into bi function and composition of the smooth endoplasmic 19<br>reticulum (Berry et al., 1985). Another study indicates<br>that insulin deficiency reduces bilirubin excretion into<br>bile (Muller-Oerlinghausen and Schenke, 1970), an ef-<br> that insulin deficiency reduces bilirubin excretion into bile (Muller-Oerlinghausen and Schenke, 1970), an effect probably owing to altered bile acid secretion. When exogenous bilirubin is injected into streptozotocin-in-<br> reticulum (Berry et al., 1985). Another study indicates<br>
teine, not the glutathione conjugate, appears in the bile of<br>
that insulin deficiency reduces bilirubin excretion into<br>
bile (Muller-Oerlinghausen and Schenke, 1970 bile (Muller-Oerlinghausen and Schenke, 1970), an ofect probably owing to altered bile acid secretion. When exogenous bilirubin is injected into streptozotocin-iduced diabetic rats, clearance of bilirubin and bilia excreti fect probably owing to altered bile acid secretion. Whe exogenous bilirubin is injected into streptozotocin-in duced diabetic rats, clearance of bilirubin and bilian excretion of monoglucuronide and diglucuronide conjugate exogenous bilirubin is injected into streptozotocin-in-<br>duced diabetic rats, clearance of bilirubin and biliary<br>excretion of monoglucuronide and diglucuronide conju-<br>gates of bilirubin are unchanged (Watkins and Sher-<br>man, duced diabetic rats, clearance of bilirubin and biliary<br>excretion of monoglucuronide and diglucuronide conju-<br>gates of bilirubin are unchanged (Watkins and Sher-<br>man, 1992). In contrast, Gonzalez and Fevery (1992)<br>report i excretion of monoglucuronide and diglucuronide conjugates of bilirubin are unchanged (Watkins and Sherman, 1992). In contrast, Gonzalez and Fevery (1992) report increased bilirubin secretion and metabolism in genetically d gates of bilirubin are unchanged (Watkins and Sheman, 1992). In contrast, Gonzalez and Fevery (199<br>report increased bilirubin secretion and metabolism<br>genetically diabetic rats, and Tunon et al. (1991) fin<br>enhanced bilirub man, 1992). In contrast, Gonzalez and Fevery (1992)<br>report increased bilirubin secretion and metabolism in<br>genetically diabetic rats, and Tunon et al. (1991) find<br>enhanced bilirubin secretion in streptozotocin-diabetic<br>ra report increased bilirubin secretion and metabolism in<br>genetically diabetic rats, and Tunon et al. (1991) find<br>enhanced bilirubin secretion in streptozotocin-diabetic<br>rats. Bile acids clearly influence the hepatic uptake a genetically diabetic rats, and Tunon et al. (1991) find<br>enhanced bilirubin secretion in streptozotocin-diabetic<br>rats. Bile acids clearly influence the hepatic uptake and<br>biliary transport of numerous cholephilic chemicals, enhanced bilirubin secretion in streptozotocin-<br>rats. Bile acids clearly influence the hepatic upt<br>biliary transport of numerous cholephilic chemic<br>the direction of the influence varies with the c<br>(Klaassen and Watkins, 19 ts. Bile acids clearly influence the hepatic uptake a<br>liary transport of numerous cholephilic chemicals,  $\theta$ <br>e direction of the influence varies with the cholep<br>laassen and Watkins, 1984; Strange, 1984).<br>In addition to b

biliary transport of numerous cholephilic chemicals, but<br>the direction of the influence varies with the cholephil ing<br>(Klaassen and Watkins, 1984; Strange, 1984).<br>In addition to bile acids, secretion of several electro-<br>l the direction of the influence varies with the cholephil  $\frac{m_1}{n_2}$  (Klaassen and Watkins, 1984; Strange, 1984). Re In addition to bile acids, secretion of several electrodity stems (Na<sup>+</sup>, bicarbonate) can increase bi (Klaassen and Watkins, 1984; Strange, 1984).<br>
In addition to bile acids, secretion of several electro-<br>
lytes (Na<sup>+</sup>, bicarbonate) can increase bile flow, and<br>
there is evidence that many of the transport systems are<br>
Na<sup></sup> In addition to bile acids, secretion of several electro-<br>lytes  $(Na^+$ , bicarbonate) can increase bile flow, and<br>there is evidence that many of the transport systems are<br> $Na^+$ -dependent. Concentrations of sodium ions incre lytes  $(Na^+$ , bicarbonate) can increase bile flow, and there is evidence that many of the transport systems are  $Na^+$ -dependent. Concentrations of sodium ions increase and bicarbonate ions decrease in diabetic bile, but p there is evidence that many of the transport systems are  $Na^+$ -dependent. Concentrations of sodium ions increase and bicarbonate ions decrease in diabetic bile, but potassium and chloride ion concentrations are unchanged  $Na<sup>+</sup>$ -dependent. Concentrations of sodium ions increase and bicarbonate ions decrease in diabetic bile, but po tassium and chloride ion concentrations are unchangee from normal (Watkins and Dykstra, 1987). The increas and bicarbonate ions decrease in diabetic bile, but potassium and chloride ion concentrations are unchanged from normal (Watkins and Dykstra, 1987). The increase in excretion of bile acids should stimulate bile acid-<br>depen tassium and chloride ion concentrations are unchan<br>from normal (Watkins and Dykstra, 1987). The incre<br>in excretion of bile acids should stimulate bile a<br>dependent bile formation, whereas the decrease in<br>carbonate ion excre from normal (Watkins and Dykstra, 1987). The increase<br>in excretion of bile acids should stimulate bile acid-<br>dependent bile formation, whereas the decrease in bi-<br>carbonate ion excretion should diminish bile acid-inde-<br>pen in excretion of bile acids should stimulate bile<br>dependent bile formation, whereas the decrease is<br>carbonate ion excretion should diminish bile acid-i<br>pendent bile formation. The available data man<br>both reduced and normal dependent bile formation, whereas the decrease in bi-<br>carbonate ion excretion should diminish bile acid-inde-<br>in pendent bile formation. The available data manifest<br>both reduced and normal bile flow rates in insulin-deficarbonate ion excretion should diminish bile acid-independent bile formation. The available data manifest both reduced and normal bile flow rates in insulin-deficient rats, which indicates that other mechanisms of bile do pendent bile formation. The available data manife<br>both reduced and normal bile flow rates in insulin-de<br>cient rats, which indicates that other mechanisms of bi<br>formation must also be considered besides the excretio<br>of osmo th reduced and normal bile flow rates in insulin-defi-<br>ent rats, which indicates that other mechanisms of bile<br>dermation must also be considered besides the excretion<br>osmotically active bile acids and inorganic solutes.<br>A

cient rats, which indicates that other mechanisms of bile<br>formation must also be considered besides the excretion<br>of osmotically active bile acids and inorganic solutes.<br>All these data indicate that many alterations in th formation must also be considered besides the excretion<br>of osmotically active bile acids and inorganic solutes.<br>All these data indicate that many alterations in the<br>biliary excretion of endogenous compounds occur during<br>pe diabetes. **C. Diabetes.**<br>
C. Diabetes-induced Alterations of the Biliary Excretion<br>
of Xenobiotics<br>
conservations of the Biliary Excretion<br>
of Xenobiotics

# *diabetes.*<br>*C. Diabetes-ind*<br>*of Xenobiotics*<br>The liver pli

C. Diabetes-induced Alterations of the Biliary Excretion of Xenobiotics a central role in extracting a wide the variety of compounds from the portal circulation before their entry into the systemic circulation. In additio C. Diabetes-induced Alterations of the Biliary Excretion et a<br>of Xenobiotics affects of<br>their plays a central role in extracting a wide<br>variety of compounds from the portal circulation before  $\frac{1}{2}$ <br>their entry into th of *Xenobiotics*<br>The liver plays a central role in extracting a wide<br>variety of compounds from the portal circulation before<br>their entry into the systemic circulation. In addition to<br>the excretion of bile acids, cholestero The liver plays a central role in extracting a wide<br>variety of compounds from the portal circulation before<br>their entry into the systemic circulation. In addition to<br>the excretion of bile acids, cholesterol, and lecithin, variety of compounds from the portal circulation before their entry into the systemic circulation. In addition to alter the excretion of bile acids, cholesterol, and lecithin, diabetes seems to affect the excretion of xen their entry into the systemic circulation. In addition to<br>the excretion of bile acids, cholesterol, and lecithin, dia-<br>betes seems to affect the excretion of xenobiotics that are<br>processed by the liver. For example, altere the excretion of bile acids, cholesterol, and lecithin, diabetes seems to affect the excretion of xenobiotics that are processed by the liver. For example, altered metabolism and excretion of acetaminophen is seen in diabe betes seems to affect the excretion of xenobiotics that are<br>processed by the liver. For example, altered metabolism of important drugs are significantly affected. It is not<br>and excretion of acetaminophen is seen in diabeti and excretion of acetaminophen is seen in diabetic rats,<br>where there is a qualitative difference in the concentra-<br>tion of the usual metabolites (Jollow et al., 1974; Siegers<br>and Schutt, 1979; Siegers et al., 1983; Watkins tion of the usual metabolites (Jollow et al., 1974; Siegers

EPATOBILIARY FUNCTION<br>than normals to the toxic effects of acetaminophen, appa<br>ently owing to an enhanced capacity for glucuronidati EPATOBILIARY FUNCTION<br>than normals to the toxic effects of acetaminophen, apparently owing to an enhanced capacity for glucuronidation<br>(Price and Jollow, 1982, 1986). However, the enhanced EPATOBILIARY FUNCTION 15<br>
than normals to the toxic effects of acetaminophen, apparently owing to an enhanced capacity for glucuronidation<br>
(Price and Jollow, 1982, 1986). However, the enhanced<br>
levels of glucuronide and s than normals to the toxic effects of acetaminophen, apparently owing to an enhanced capacity for glucuronidation (Price and Jollow, 1982, 1986). However, the enhanced levels of glucuronide and sulfate conjugates are excret than normals to the toxic effects of acetaminophen, apparently owing to an enhanced capacity for glucuronidation (Price and Jollow, 1982, 1986). However, the enhanced levels of glucuronide and sulfate conjugates are excret ently owing to an enhanced capacity for glucuronidation (Price and Jollow, 1982, 1986). However, the enhanced levels of glucuronide and sulfate conjugates are excreted preferentially in the urine of diabetics, resulting in (Price and Jollow, 1982, 1986). However, the enhanced<br>levels of glucuronide and sulfate conjugates are excreted<br>preferentially in the urine of diabetics, resulting in de-<br>creased levels of these metabolites in bile (Sieger levels of glucuronide and sulfate conjugates are excreted<br>preferentially in the urine of diabetics, resulting in de-<br>creased levels of these metabolites in bile (Siegers et al.,<br>1985; Watkins and Sherman, 1992). In additio preferentially in the urine of diabetics, resulting in decreased levels of these metabolites in bile (Siegers et al., 1985; Watkins and Sherman, 1992). In addition, the cysteine, not the glutathione conjugate, appears in creased levels of these metabolites in bile (Siegers et 1985; Watkins and Sherman, 1992). In addition, the c<br>teine, not the glutathione conjugate, appears in the bile<br>diabetic rats, indicating an enhanced breakdown of<br>glu 1985; Watkins and Sherman, 19<br>teine, not the glutathione conjug<br>diabetic rats, indicating an enh<br>glutathione conjugate by<br>(Watkins and Sherman, 1992).<br>Likewise, decreased fecal and ine, not the glutathione conjugate, appears in the bilar<br>abetic rats, indicating an enhanced breakdown of intathione conjugate by  $\gamma$ -glutamyltranspeptidities<br>abetic metab-<br>Likewise, decreased fecal and biliary levels of

eliminated primarily as ester and ether glucuronides, is<br>
C. Diabetes-induced Alterations of the Biliary Excretion<br>
of and the streptozotocin-diabetic rats (Lin<br>
of Xenobiotics<br>
of Xenobiotics<br>
of Menobiotics<br>
of the liver diabetic rats, indicating an enhanced breakdown of the<br>glutathione conjugate by  $\gamma$ -glutamyltranspeptidase<br>(Watkins and Sherman, 1992).<br>Likewise, decreased fecal and biliary levels of metab-<br>olites of diazepam are observ glutathione conjugate by  $\gamma$ -glutamyltranspeptidase (Watkins and Sherman, 1992).<br>Likewise, decreased fecal and biliary levels of metabolites of diazepam are observed in 1-day diabetic rats after its oral administration ( (Watkins and Sherman, 1992).<br>
Likewise, decreased fecal and biliary levels of metabolites of diazepam are observed in 1-day diabetic rat<br>
after its oral administration (Andrews and Griffiths<br>
1984). Though highly metaboliz Likewise, decreased fecal and biliary levels of m<br>olites of diazepam are observed in 1-day diabetic<br>after its oral administration (Andrews and Grif<br>1984). Though highly metabolized by both phase I<br>ethylation and hydroxylat olites of diazepam are observed in 1-day diabetic rats<br>after its oral administration (Andrews and Griffiths,<br>1984). Though highly metabolized by both phase I dem-<br>ethylation and hydroxylation and phase II glucuronida-<br>tion after its oral administration (Andrews and Griffiths, 1984). Though highly metabolized by both phase I demethylation and hydroxylation and phase II glucuronidation reactions before its excretion via the biliary route, no d 1984). Though highly metabolized by both phase I demethylation and hydroxylation and phase II glucuronidation reactions before its excretion via the biliary route, no differences in the metabolism of diazepam are observed. ethylation and hydroxylation and phase II glucuronidation reactions before its excretion via the biliary route, no differences in the metabolism of diazepam are observed. The unchanged cardiac glycosides digoxin and ouabai tion reactions before its excretion via the biliary route,<br>no differences in the metabolism of diazepam are ob-<br>served. The unchanged cardiac glycosides digoxin and<br>ouabain undergo very little biotransformation before be-<br> no differences in the metabolism of diazepam are observed. The unchanged cardiac glycosides digoxin and ouabain undergo very little biotransformation before being excreted into the bile (Russell and Klaassen, 1973). Recent served. The unchanged cardiac glycosides digoxin and<br>ouabain undergo very little biotransformation before be-<br>ing excreted into the bile (Russell and Klaassen, 1973).<br>Recent studies have shown that biliary excretion of bot ouabain undergo very little biotransformation before be-<br>ing excreted into the bile (Russell and Klaassen, 1973).<br>Recent studies have shown that biliary excretion of both<br>digoxin (Watkins and Sherman, 1992) and ouabain<br>(Wa ing excreted into the bile (Russell and Klaassen, 1973).<br>Recent studies have shown that biliary excretion of both<br>digoxin (Watkins and Sherman, 1992) and ouabain<br>(Watkins and Dykstra, 1987) is increased in diabetic<br>rats, i Recent studies have shown that biliary excretion of both<br>digoxin (Watkins and Sherman, 1992) and ouabain<br>(Watkins and Dykstra, 1987) is increased in diabetic<br>rats, in spite of an unchanged rate of bile flow. Watkins<br>and Dy digoxin (Watkins and Sherman, 1992) and ouabain<br>(Watkins and Dykstra, 1987) is increased in diabetic<br>rats, in spite of an unchanged rate of bile flow. Watkins<br>and Dykstra (1987) find that total and biliary clearance<br>of an (Watkins and Dykstra, 1987) is increased in diabetic rats, in spite of an unchanged rate of bile flow. Watkins and Dykstra (1987) find that total and biliary clearance of an organic cation procainamide ethobromide, uncharg rats, in spite of an unchanged rate of bile flow. Watkin<br>and Dykstra (1987) find that total and biliary clearanc<br>of an organic cation procainamide ethobromide, un<br>charged ouabain, and the bile acid taurocholate are en<br>hanc and Dykstra (1987) find that total and biliary clearance<br>of an organic cation procainamide ethobromide, un-<br>charged ouabain, and the bile acid taurocholate are en-<br>hanced by diabetes, whereas clearance of the bile acid-<br>in charged ouabain, and the bile acid taurocholate are enhanced by diabetes, whereas clearance of the bile acid-<br>independent anion phenol red is apparently not affected.<br>Further differentiation indicates that the bile flow ra charged ouabain, and the bile acid taurocholate are  $\alpha$  hanced by diabetes, whereas clearance of the bile acid-independent anion phenol red is apparently not affect Further differentiation indicates that the bile flow ri hanced by diabetes, whereas clearance of the bile acid<br>independent anion phenol red is apparently not affected<br>Further differentiation indicates that the bile flow rat<br>in diabetics is unchanged by the bile acid-independen<br> independent anion phenol red is apparently not affected<br>Further differentiation indicates that the bile flow rat<br>in diabetics is unchanged by the bile acid-independen<br>organic anions (eosin, amaranth, and phenol-3, 6-di<br>bro Further differentiation indicates that the bile flow rate<br>in diabetics is unchanged by the bile acid-independent<br>organic anions (eosin, amaranth, and phenol-3, 6-di-<br>bromphthalein disulfonate) but that certain bile acid-<br>d in diabetics is unchanged by the bile acid-independent<br>organic anions (eosin, amaranth, and phenol-3, 6-di-<br>bromphthalein disulfonate) but that certain bile acid-<br>dependent anions (bromcresol green, indocyanine green<br>and r organic anions (eosin, amaranth, and phenol-3, 6-di-<br>bromphthalein disulfonate) but that certain bile acid-<br>dependent anions (bromcresol green, indocyanine green<br>and rose bengal) are choleretic (Watkins and Noda,<br>1986). Oe gentamicin. Finally, diflunisal, a fluorinated salicylate dependent anions (bromcresol green, indocyanine green<br>and rose bengal) are choleretic (Watkins and Noda,<br>1986). Oehler and coworkers (1989) show that non-mi-<br>celle-forming bile acids increase the biliary excretion of<br>genta and rose bengal) are choleretic (Watkins and Noda, 1986). Oehler and coworkers (1989) show that non-micelle-forming bile acids increase the biliary excretion of gentamicin. Finally, diflunisal, a fluorinated salicylate wit 1986). Oehler and coworkers (1989) show that non-micelle-forming bile acids increase the biliary excretion of gentamicin. Finally, diflunisal, a fluorinated salicylate with nonsteroidal anti-inflammatory properties that is celle-forming bile acids increase the biliary excretion of<br>gentamicin. Finally, diflunisal, a fluorinated salicylate<br>with nonsteroidal anti-inflammatory properties that is<br>eliminated primarily as ester and ether glucuronid gentamicin. Finally, diflunisal, a fluorinated salicylate<br>with nonsteroidal anti-inflammatory properties that is<br>eliminated primarily as ester and ether glucuronides, is<br>cleared more rapidly by streptozotocin-diabetic rats et al., 1989). It seems from these data that diabetes must eliminated primarily as ester a<br>cleared more rapidly by strepto:<br>et al., 1989). It seems from these<br>affect the activity of various of<br>these chemicals into the bile.<br>In spite of these published ef eared more rapidly by streptozotocin-diabetic rats (Lin al., 1989). It seems from these data that diabetes must<br>fect the activity of various carriers for transport of<br>see chemicals into the bile.<br>In spite of these publishe

et al., 1989). It seems from these data that diabetes must<br>affect the activity of various carriers for transport of<br>these chemicals into the bile.<br>In spite of these published effects of diabetes-induced<br>alterations in the affect the activity of various carriers for transport<br>these chemicals into the bile.<br>In spite of these published effects of diabetes-induc<br>alterations in the biliary excretion of xenobiotics, the<br>are few epidemiological st these chemicals into the bile.<br>In spite of these published effects of diabetes-induce<br>alterations in the biliary excretion of xenobiotics, there<br>are few epidemiological studies that unequivocally demon<br>strate that the phar In spite of these published effects of diabetes-induced<br>alterations in the biliary excretion of xenobiotics, there<br>are few epidemiological studies that unequivocally demon-<br>strate that the pharmacodynamics and pharmacokine alterations in the biliary excretion of xenobiotics, the are few epidemiological studies that unequivocally dem strate that the pharmacodynamics and pharmacokine of important drugs are significantly affected. It is known w are few epidemiological studies that unequivocally demostrate that the pharmacodynamics and pharmacokinet of important drugs are significantly affected. It is reproved to the movement of the movement diabetic patients are strate that the pharmacodynamics and pharmacokinetics<br>of important drugs are significantly affected. It is not<br>known whether type I insulin-dependent or type II insulin-<br>independent diabetic patients are idiosyncratically of important drugs are significantly affected. It is not known whether type I insulin-dependent or type II insulin-<br>independent diabetic patients are idiosyncratically hyper-<br>responsive or hyporesponsive to any drug treatm known whether type I insulin-dependeer<br>independent diabetic patients are idioresponsive or hyporesponsive to any<br>some fashion that suggests a disease-i<br>ture work must address this concern.

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# VIII. **Effect of Insulin-mimetic Agents on Hepatic Function**

WATKINS ANI<br>III. **Effect of Insulin-mimetic Agents on Hepatic**<br>**Function**<br>Vanadium salts (Nechay, 1984; Nechay et al., 1985;<br>lechter, 1990), peroxovanadium compounds (Fantus et **VIII. Effect of Insulin-mimetic Agents on Hepatic**<br> **Function**<br>
Vanadium salts (Nechay, 1984; Nechay et al., 1985;<br>
Shechter, 1990), peroxovanadium compounds (Fantus et al., 1989; Leighton et al., 1991), selenite (Ezaki, **Function**<br>**Function**<br>Vanadium salts (Nechay, 1984; Nechay et al., 1985;<br>Shechter, 1990), peroxovanadium compounds (Fantus et<br>al., 1989; Leighton et al., 1991), selenite (Ezaki, 1990),<br>molybdate and tungstate (Goto et al., Function<br>
Vanadium salts (Nechay, 1984; Nechay et al., 1985; to in<br>
Shechter, 1990), peroxovanadium compounds (Fantus et med<br>
al., 1989; Leighton et al., 1991), selenite (Ezaki, 1990), is n<br>
molybdate and tungstate (Goto e Vanadium salts (Nechay, 1984; Nechay et al., 1985; Shechter, 1990), peroxovanadium compounds (Fantus et al., 1989; Leighton et al., 1991), selenite (Ezaki, 1990), implybdate and tungstate (Goto et al., 1992), zinc ion (Sh al., 1989; Leighton et al., 1991), selenite (Ezaki, 1990),  $\frac{16}{100}$  molybdate and tungstate (Goto et al., 1992), zinc ion (Shisheva et al., 1992), and chromium (Singh et al.,  $\frac{1}{100}$  molybdate mimics insulin is 19 molybdate and tungstate (Goto et al., 1992), zinc ion<br>(Shisheva et al., 1992), and chromium (Singh et al.,<br>1992) can all exert insulin-like effects in vitro. Although<br>the mechanism by which vanadate mimics insulin is<br>ill-d 1992) can all exert insulin-like effects in vitro. Although<br>the mechanism by which vanadate mimics insulin is<br>ill-defined, much data support a theory that vanadate<br>activates glucose metabolism by an insulin-independent<br>mec the mechanism by which vanadate mimics insulin is<br>ill-defined, much data support a theory that vanadate<br>activates glucose metabolism by an insulin-independent<br>mechanism or by skirting the early events of the insulin-<br>depen the mechanism by which vanadate mimics insulin is<br>ill-defined, much data support a theory that vanadate<br>activates glucose metabolism by an insulin-independent<br>mechanism or by skirting the early events of the insulin-<br>depen ill-defined, much<br>activates glucose r<br>mechanism or by s<br>dependent cascade<br>Shechter, 1990).<br>Oral administra tivates glucose metabolism by an insulin-independent<br>echanism or by skirting the early events of the insulin-<br>pendent cascade (Nechay, 1984; Nechay et al., 1985;<br>echter, 1990).<br>Oral administration of orthovanadate partiall

mechanism or by skirting the early events of the inseparation of scheme as<br>cade (Nechay, 1984; Nechay et al., Shechter, 1990).<br>Oral administration of orthovanadate partially<br>malizes blood glucose concentrations in streptoz dependent cascade (Nechay, 1984; Nechay et al., 1985;<br>Shechter, 1990).<br>Oral administration of orthovanadate partially nor-<br>malizes blood glucose concentrations in streptozotocin-<br>induced diabetic rats (Brichard et al., 198 Shechter, 1990).<br>
Oral administration of orthovanadate partially nor-<br>
malizes blood glucose concentrations in streptozotocin-<br>
induced diabetic rats (Brichard et al., 1988; Cam et al.,<br>
1993; Challiss et al., 1987; Heylig Oral administration of orthovanadate partially n<br>malizes blood glucose concentrations in streptozotoc<br>induced diabetic rats (Brichard et al., 1988; Cam et a<br>1993; Challiss et al., 1987; Heyliger et al., 1985; I<br>gazhenthi malizes blood glucose concentrations in streptozotocin-<br>induced diabetic rats (Brichard et al., 1988; Cam et al.,<br>1993; Challiss et al., 1987; Heyliger et al., 1985; Pu-<br>gazhenthi and Khandelwal, 1990) or in insulin-resist induced diabetic rats (Brichard et al., 1988; Cam et al., 1993; Challiss et al., 1987; Heyliger et al., 1985; Pugazhenthi and Khandelwal, 1990) or in insulin-resistant diabetic  $ob/ob$  mice (Brichard et al., 1990) and resto 1993; Challiss et al., 1987; Heyliger et al., 1985; Pugazhenthi and Khandelwal, 1990) or in insulin-resistant<br>diabetic  $ob/ob$  mice (Brichard et al., 1990) and restores<br>cholesterol, phospholipid, and triglyceride levels in<br> diabetic  $ob/ob$  mice (Brichard et al., 1990) and restores the cholesterol, phospholipid, and triglyceride levels in plasma lipoprotein fractions to near normal levels in (Sekar and Govindasamy, 1991). Treatment of diabetic cholesterol, phospholipid, and triglyceride levels in plasma lipoprotein fractions to near normal levels (Sekar and Govindasamy, 1991). Treatment of diabetic rats with vanadyl sulfate augments peripheral glucose utilizatio plasma lipoprotein fractions to near normal levels<br>(Sekar and Govindasamy, 1991). Treatment of diabetic<br>rats with vanadyl sulfate augments peripheral glucose<br>utilization, independently of insulin-receptor kinase ac-<br>tivity (Sekar and Govindasamy, 1991). Treatment of diabetic rats with vanadyl sulfate augments peripheral glucose utilization, independently of insulin-receptor kinase activity (Venkatesan et al., 1991). Moreover, oral vanadate rats with vanadyl sulfate augments peripheral glu<br>utilization, independently of insulin-receptor kinas<br>tivity (Venkatesan et al., 1991). Moreover, oral vana<br>therapy over 2 months reduces glycosylated hemogl<br>levels, activat utilization, independently of insulin-receptor kinase activity (Venkatesan et al., 1991). Moreover, oral vanadate<br>therapy over 2 months reduces glycosylated hemoglobin<br>levels, activates glycolysis, and depresses gluconeoge tivity (Venkatesan et al., 1991). Moreover, oral vanadate<br>therapy over 2 months reduces glycosylated hemoglobin<br>levels, activates glycolysis, and depresses gluconeogen-<br>esis in streptozotocin-induced diabetic rats (Sekar e therapy over 2 months reduces glycosylated hemoglo<br>levels, activates glycolysis, and depresses gluconeog<br>esis in streptozotocin-induced diabetic rats (Sekar et<br>1990). Lipoprotein lipase and hepatic lipase activii<br>are corre levels, activates glycolysis, and depresses glucon<br>esis in streptozotocin-induced diabetic rats (Sekai<br>1990). Lipoprotein lipase and hepatic lipase ac<br>are corrected toward normal values after oral ac<br>tration of sodium meta esis in streptozotocin-induced diabetic rats (Sekar et al., 1990). Lipoprotein lipase and hepatic lipase activities are corrected toward normal values after oral administration of sodium metavanadate to streptozotocin-diab 1990). Lipoprotein lipase and hepatic lipase activities here corrected toward normal values after oral administration of sodium metavanadate to streptozotocin-diabetic rats (Levy and Bendayan, 1991). These studies Kn prov are corrected toward normal values after oral adminitration of sodium metavanadate to streptozotocin-dibetic rats (Levy and Bendayan, 1991). These studiprovide evidence that dietary orthovanadate can asomewhat effective as tes. tic rats (Levy and Bendayan, 1991). These study or evidence that dietary orthovanadate can mewhat effective as an oral agent for treating din s.<br>The first study to examine whether oral orthovite therapy normalizes diabetes

provide evidence that dietary orthovanadate can be toxis somewhat effective as an oral agent for treating diabetes.<br>
The first study to examine whether oral orthovana-<br>
date therapy normalizes diabetes-induced alterations somewhat effective as an oral agent for treating diabetes.<br>
the first study to examine whether oral orthovana-<br>
date therapy normalizes diabetes-induced alterations in<br>
hepatobiliary function notes that the increased total tes.<br>The first study to examine whether oral orthovana-<br>date therapy normalizes diabetes-induced alterations in<br>hepatobiliary function notes that the increased total and<br>biliary clearances of rose bengal in diabetic rats The first study to examine whether oral orthovana-<br>date therapy normalizes diabetes-induced alterations in<br>hepatobiliary function notes that the increased total and<br>biliary clearances of rose bengal in diabetic rats 4 week date therapy normalizes diabetes-induced alteration<br>hepatobiliary function notes that the increased total<br>biliary clearances of rose bengal in diabetic rats 4 we<br>after streptozotocin treatment are not reversed by<br>thovanada hepatobiliary function notes that the increased total an<br>biliary clearances of rose bengal in diabetic rats 4 week<br>after streptozotocin treatment are not reversed by or<br>thovanadate therapy. Moreover, oral sodium orthovana<br> biliary clearances of rose bengal in diabetic rats 4 weeks<br>after streptozotocin treatment are not reversed by or-<br>thovanadate therapy. Moreover, oral sodium orthovana-<br>date does not completely reverse diabetes-induced alte after streptozotocin treatment are not reversed by orthovanadate therapy. Moreover, oral sodium orthovanadate does not completely reverse diabetes-induced alterations of basal bile acid excretion (Watkins et al., 1993). Fi thovanadate therapy. Moreover, oral sodium orthovana-<br>date does not completely reverse diabetes-induced alter-<br>ations of basal bile acid excretion (Watkins et al., 1993).<br>Finally, bile formation is not reduced, suggesting date does not completely reverse diabetes-induced alte<br>ations of basal bile acid excretion (Watkins et al., 1993<br>Finally, bile formation is not reduced, suggesting tha<br>the dose of orthovanadate was too low to compromis<br>hep ations of basal bile acid excretion (Watkins et al., 1993).<br>Finally, bile formation is not reduced, suggesting that<br>the dose of orthovanadate was too low to compromise<br>hepatic perfusion and oxygen consumption. The vana-<br>da Finally, bile formation is not reduced, suggesting that<br>the dose of orthovanadate was too low to compromise<br>hepatic perfusion and oxygen consumption. The vana-<br>date-induced reduction in bile flow rate is apparently<br>owing t the dose of orthovanadate was too low to compromise<br>hepatic perfusion and oxygen consumption. The vana-<br>date-induced reduction in bile flow rate is apparently<br>owing to hypoxia caused by the direct action on vascular<br>mooth hepatic perfusion and oxygen consumption. The vana-<br>date-induced reduction in bile flow rate is apparently wowing to hypoxia caused by the direct action on vascular no<br>smooth muscle resulting in decreased vascular perfusi date-induced reduction in bile flow rate is apparently wowing to hypoxia caused by the direct action on vascular nesselves about the smooth muscle resulting in decreased vascular perfusion is and not to any inhibition of owing to hypoxia caused by the direct action on vasos<br>smooth muscle resulting in decreased vascular perfu<br>and not to any inhibition of Na<sup>+</sup>-K<sup>+</sup>-ATPase (Thon<br>and Larsen, 1982b), an enzyme involved in production<br>the bile a nooth muscle resulting in decreased vascular perfusion of not to any inhibition of Na<sup>+</sup>-K<sup>+</sup>-ATPase (Thoms d Larsen, 1982b), an enzyme involved in production e bile acid-independent fraction of bile secretion.<br>Recent wor

and not to any inhibition of Na<sup>+</sup>-K<sup>+</sup>-ATPase (Thomsend Larsen, 1982b), an enzyme involved in production<br>the bile acid-independent fraction of bile secretion.<br>Recent work demonstrates that an alternative biosy<br>thetic pat and Larsen, 1982b), an enzyme involved in production of<br>the bile acid-independent fraction of bile secretion. i<br>Recent work demonstrates that an alternative biosyn-<br>thetic pathway of cholic acid via  $3\alpha$ , 7 $\alpha$ -dihydroxy

of oral vanadate treatment partially cancels the in-<br>creased cholic acid production in diabetic rats similarly COM SANDERS<br>of oral vanadate treatment partially cancels the in-<br>creased cholic acid production in diabetic rats similarly<br>to insulin therapy (Kimura et al., 1992). Although the EXANDERS<br>of oral vanadate treatment partially cancels the in-<br>creased cholic acid production in diabetic rats similarly<br>to insulin therapy (Kimura et al., 1992). Although the<br>mechanism by which vanadate alters bile acid me mechanism by analysis and the increased cholic acid production in diabetic rats similarly to insulin therapy (Kimura et al., 1992). Although the mechanism by which vanadate alters bile acid metabolism is not fully understo of oral vanadate treatment partially cancels the in-<br>creased cholic acid production in diabetic rats similarly<br>to insulin therapy (Kimura et al., 1992). Although the<br>mechanism by which vanadate alters bile acid metabolism<br> creased cholic acid production in diabetic rats similarly<br>to insulin therapy (Kimura et al., 1992). Although the<br>mechanism by which vanadate alters bile acid metabolism<br>is not fully understood, vanadate does not increase s to insulin therapy (Kimura et al., 1992). Alection<br>mechanism by which vanadate alters bile acid<br>is not fully understood, vanadate does not inca<br>insulin concentrations and is not functioning<br>lin-dependent pathway (Ogura et echanism by which vanadate alters bile acid metabo<br>not fully understood, vanadate does not increase se<br>sulin concentrations and is not functioning via an i<br>--dependent pathway (Ogura et al., 1991).<br>Unfortunately, all forms

is not fully understood, vanadate does not increase serum<br>insulin concentrations and is not functioning via an insu-<br>lin-dependent pathway (Ogura et al., 1991).<br>Unfortunately, all forms of oral vanadate (metavana-<br>date, or insulin concentrations and is not functioning via an insu-<br>lin-dependent pathway (Ogura et al., 1991).<br>Unfortunately, all forms of oral vanadate (metavana-<br>date, orthovanadate or vanadyl sulfate) elicit toxicity in<br>rats th lin-dependent pathway (Ogura et al., 1991).<br>Unfortunately, all forms of oral vanadate (metavana-<br>date, orthovanadate or vanadyl sulfate) elicit toxicity in<br>rats that ranges from decreased weight gain and in-<br>creased serum Unfortunately, all forms of oral vanadate (metavana-<br>date, orthovanadate or vanadyl sulfate) elicit toxicity in<br>rats that ranges from decreased weight gain and in-<br>creased serum concentrations of urea and creatinine to<br>dea date, orthovanadate or vanadyl sulfate) elicit toxicity is<br>rats that ranges from decreased weight gain and in<br>creased serum concentrations of urea and creatinine t<br>death (Domingo et al., 1991; Mongold et al., 1990). Use c<br> rats that ranges from decreased weight gain and increased serum concentrations of urea and creatinine to death (Domingo et al., 1991; Mongold et al., 1990). Use of vanadium salts as adjuncts to insulin therapy for insulincreased serum concentrations of urea and creatinine to<br>death (Domingo et al., 1991; Mongold et al., 1990). Use of<br>vanadium salts as adjuncts to insulin therapy for insu-<br>lin-dependent diabetic patients must carefully balan death (Domingo et al., 1991; Mongold et al., 1990). Use of vanadium salts as adjuncts to insulin therapy for insulin-dependent diabetic patients must carefully balance<br>therapeutic versus toxic actions of the agents. The ch vanadium salts as adjuncts to insulin therapy for insulin-dependent diabetic patients must carefully balance<br>therapeutic versus toxic actions of the agents. The che-<br>lator Tiron seems to ameliorate the toxic effects of van lin-dependent diabetic patients must care<br>therapeutic versus toxic actions of the age<br>lator Tiron seems to ameliorate the toxic e<br>adate and to diminish the accumulation of<br>kidney and bone (Domingo et al., 1992).<br>Moreover, erapeutic versus toxic actions of the agents. The che-<br>tor Tiron seems to ameliorate the toxic effects of van-<br>ate and to diminish the accumulation of vanadium in<br>dney and bone (Domingo et al., 1992).<br>Moreover, the effect

adate and to diminish the accumulation of vanadium in<br>kidney and bone (Domingo et al., 1992).<br>Moreover, the effect of combined therapies (insulin<br>plus vanadate) on hepatic function has yet to be ascer-<br>tained. Low-dose van adate and to diminish the accumulation of vanadium in<br>kidney and bone (Domingo et al., 1992).<br>Moreover, the effect of combined therapies (insulin<br>plus vanadate) on hepatic function has yet to be ascer-<br>tained. Low-dose van kidney and bone (Domingo et al., 1992).<br>Moreover, the effect of combined therapies (insulin<br>plus vanadate) on hepatic function has yet to be ascer-<br>tained. Low-dose vanadate plus insulin therapy may-<br>prove to be beneficial Moreover, the effect of combined therapies (insulin<br>plus vanadate) on hepatic function has yet to be ascer-<br>tained. Low-dose vanadate plus insulin therapy may<br>prove to be beneficial; therefore, continued study is war-<br>rant plus vanadate) on hepatic function has yet to be ascentained. Low-dose vanadate plus insulin therapy m<br>prove to be beneficial; therefore, continued study is warented. The efficacy of combining other insulinomime<br>agents wit tained. Low-dose vanadate plus insulin therapy may<br>prove to be beneficial; therefore, continued study is war-<br>ranted. The efficacy of combining other insulinomimetic<br>agents with insulin also needs to be examined. Combi-<br>na prove to be beneficial; therefore, continued study is warranted. The efficacy of combining other insulinomimetic agents with insulin also needs to be examined. Combination of sodium orthovanadate with ascorbic acid could h ranted. The efficacy of combinine<br>agents with insulin also needs<br>nation of sodium orthovanadate<br>have beneficial effects by redu<br>diabetes (Young et al., 1992). In orthovanadate with asceffects by reducing oxidency of the set of the USA.<br>IX. Future Directions tv of both diabetes mell have beneficial effects by reducing oxidative stress in<br>diabetes (Young et al., 1992).<br>**IX. Future Directions**<br>The complexity of both diabetes mellitus as well as<br>hepatic biochemistry and physiology contribute to the

diabetes (Young et al., 1992).<br> **IX. Future Directions**<br>
The complexity of both diabetes mellitus as well as<br>
hepatic biochemistry and physiology contribute to the<br>
difficult task of understanding the effects of insulin de IX. Future Directions<br>The complexity of both diabetes mellitus as well as<br>hepatic biochemistry and physiology contribute to the<br>difficult task of understanding the effects of insulin de-<br>ficiency on biotransformation and b ficiency on biotransformation and biliary excretion. The complexity of both diabetes mellitus as well as<br>hepatic biochemistry and physiology contribute to the<br>difficult task of understanding the effects of insulin de<br>ficiency on biotransformation and biliary excretion<br>Knowin hepatic biochemistry and physiology contribute to t<br>difficult task of understanding the effects of insulin c<br>ficiency on biotransformation and biliary excretic<br>Knowing that both alloxan and streptozotocin are cy<br>toxic, we difficult task of understanding the effects of insulin deficiency on biotransformation and biliary excretion.<br>Knowing that both alloxan and streptozotocin are cytotoxic, we need to ascertain what, if any, ultrastructural c ficiency on biotransformation and biliary excretion.<br>Knowing that both alloxan and streptozotocin are cyto-<br>toxic, we need to ascertain what, if any, ultrastructural<br>changes occur and how these relate to the observed<br>funct Knowing that both alloxan and streptozotocin are cyto-<br>toxic, we need to ascertain what, if any, ultrastructural<br>changes occur and how these relate to the observed<br>functional differences. Because many metabolic en-<br>zymes w toxic, we need to ascertain what, if any, ultrastructure<br>changes occur and how these relate to the observ<br>functional differences. Because many metabolic e<br>zymes whose functions are influenced by diabetes resi<br>in the micros changes occur and how these relate to the observed<br>functional differences. Because many metabolic en-<br>zymes whose functions are influenced by diabetes reside<br>in the microsomal fraction, changes in glycogen, choles-<br>terol, functional differences. Because many metabolic entry express whose functions are influenced by diabetes residentian the microsomal fraction, changes in glycogen, chole terol, and phospholipid levels could influence either zymes whose functions are influenced by diabetes reside in the microsomal fraction, changes in glycogen, choles terol, and phospholipid levels could influence either transport mechanisms or enzymes bound in the membranes o malemma. terol, and phospholipid levels could influence either<br>transport mechanisms or enzymes bound in the mem-<br>branes of mitochondria, endoplasmic reticulum, or plas-<br>malemma.<br>Whereas specific alterations in phase I cytochrome<br>P4

transport mechanisms or enzymes bound in the mem-<br>branes of mitochondria, endoplasmic reticulum, or plas-<br>malemma.<br>Whereas specific alterations in phase I cytochrome<br>P450 isozymes have been demonstrated, similar studies<br>on branes of mitochondria, endoplasmic reticulum, or plas-<br>malemma.<br>Whereas specific alterations in phase I cytochrome<br>P450 isozymes have been demonstrated, similar studies<br>on the expression of specific phase II isozymes of N malemma.<br>
Whereas specific alterations in phase I cyt<br>
P450 isozymes have been demonstrated, similar<br>
on the expression of specific phase II isozym<br>
acetyltransferase, the UDP-glucuronosyltran<br>
glutathione S-transferases, Whereas specific alterations in phase I cytochrome P450 isozymes have been demonstrated, similar studies<br>on the expression of specific phase II isozymes of N-<br>acetyltransferase, the UDP-glucuronosyltransferases,<br>glutathion on the expression of specific phase II isozymes of N-<br>acetyltransferase, the UDP-glucuronosyltransferases,<br>glutathione S-transferases, or sulfotransferases are<br>warranted. No one has yet proven whether restoration of<br>normog acetyltransferase, the UDP-glucuronosyltransferases,<br>glutathione S-transferases, or sulfotransferases are<br>warranted. No one has yet proven whether restoration of<br>normoglycemia, suppression of glucagon secretion or<br>simply e glutathione S-transferases, or sulfotransferases are<br>warranted. No one has yet proven whether restoration of<br>normoglycemia, suppression of glucagon secretion of<br>simply elevation of plasma insulin concentrations is the<br>acti arranted. No one has yet proven whether restoration of<br>rrmoglycemia, suppression of glucagon secretion or<br>mply elevation of plasma insulin concentrations is the<br>tive factor in the normalization of enzyme activities.<br>Applic normoglycemia, suppression of glucagon secretion or<br>simply elevation of plasma insulin concentrations is the<br>active factor in the normalization of enzyme activities.<br>Applicability of short-term and long-term chemically<br>ind

simply elevation of plasma insulin concentrations is the active factor in the normalization of enzyme activities.<br>Applicability of short-term and long-term chemically induced animal models for human diabetes needs to be de active factor in the normalization of enzyme activities.<br>Applicability of short-term and long-term chemically<br>induced animal models for human diabetes needs to be<br>determined. The cholestasis that is seen in short-term<br>stre induced animal models for human diabetes needs to be determined. The cholestasis that is seen in short-term streptozotocin-induced diabetic rats but is absent in chronic long-term diabetic rats is not prevalant in hu-

**a**spet

DIABETES MELLITUS AN<br>man diabetics. Data are needed to unequivocally dem-<br>onstrate whether the cholestasis seen the first few day DIABETES MELLITUS AND HE<br>man diabetics. Data are needed to unequivocally dem-<br>onstrate whether the cholestasis seen the first few days<br>after streptozotocin administration is owing to the hep-DIABETES MELLITUS ANI<br>man diabetics. Data are needed to unequivocally dem-<br>onstrate whether the cholestasis seen the first few days<br>after streptozotocin administration is owing to the hep-<br>atotoxic effects of the diabetoge man diabetics. Data are needed to unequivocally demonstrate whether the cholestasis seen the first few days after streptozotocin administration is owing to the hepatotoxic effects of the diabetogen and whether effects obse man diabetics. Data are needed to unequivocally onstrate whether the cholestasis seen the first few after streptozotocin administration is owing to the atotoxic effects of the diabetogen and whether ef observed a month or onstrate whether the cholestasis seen the first few days<br>after streptozotocin administration is owing to the hep-<br>atotoxic effects of the diabetogen and whether effects<br>observed a month or more after diabetogen administraafter streptozotocin administration is owing to the hepatotoxic effects of the diabetogen and whether effects observed a month or more after diabetogen administration are owing to insulin-deficiency and not to a delayed to atotoxic effects of the diabetogen and whether effects<br>observed a month or more after diabetogen administra-<br>tion are owing to insulin-deficiency and not to a delayed<br>toxic response to the diabetogen. Use of one or several observed a month or more after diabetogen administration are owing to insulin-deficiency and not to a delayed<br>toxic response to the diabetogen. Use of one or several and<br>other animal models for both insulin-dependent and tion are owing to in<br>toxic response to the<br>other animal model<br>sulin-independent<br>solve this problem.<br>Besides laborato other animal models for both insulin-dependent and insulin-independent diabetes (Shafrir, 1990) might help<br>solve this problem.<br>Besides laboratory animals, additional work must sulin-independent diabetes (Shafrir, 1990) might help

evaluate drug disposition in diabetic patients. Moreover,<br>studies should distinguish between type I insulin-depen-<br>dent and type II insulin-independent diabetes and also<br>between patients controlled on low versus high doses solve this problem.<br>
Besides laboratory animals, additional work must<br>
evaluate drug disposition in diabetic patients. Moreover,<br>
studies should distinguish between type I insulin-dependent<br>
dent and type II insulin-indep Besides laboratory animals, additional work must  $A$ <sup>M</sup><br>evaluate drug disposition in diabetic patients. Moreover,<br>studies should distinguish between type I insulin-depen-<br>dent and type II insulin-independent diabetes and studies should distinguish between type I insulin-dependent and type II insulin-independent diabetes and also between patients controlled on low versus high doses of insulin. The potential linkages between hepatic choleste studies should distinguish between type I insulin-dependent and type II insulin-independent diabetes and also  $\frac{PR}{AND}$ <br>between patients controlled on low versus high doses of insulin. The potential linkages between hepat dent and type II insulin-independent diabetes and also<br>between patients controlled on low versus high doses of<br>insulin. The potential linkages between hepatic choles-<br>terol metabolism with cholelithiasis and gallstones and between patients controlled on low versus high doses of<br>insulin. The potential linkages between hepatic choles-<br>terol metabolism with cholelithiasis and gallstones and<br>with atheroma must also be discerned. Finally, studies insulin. The potential linkages between hepatic choles-<br>terol metabolism with cholelithiasis and gallstones and<br>with atheroma must also be discerned. Finally, studies<br>in chronic diabetics with neuropathy may enable de-<br>scr terol metabolism with cholelithiasis and gallstones and<br>with atheroma must also be discerned. Finally, studies<br>in chronic diabetics with neuropathy may enable de-<br>scription of problems in hepatobiliary function, deriving<br>f with atheroma must also be discerned. Finally, studin chronic diabetics with neuropathy may enable description of problems in hepatobiliary function, derivity from neuropathy, that are superimposed upon initi-<br>low-dose ins in chronic diabetics with neuropathy may enable description of problems in hepatobiliary function, deriving from neuropathy, that are superimposed upon initial individual behavior dose insulin effects. Obviously, the impa scription of problems in hepatobiliary function, deriving<br>from neuropathy, that are superimposed upon initial<br>low-dose insulin effects. Obviously, the impact of multi-<br>ple organ systems on hepatobiliary function must be<br>de from neuropa<br>low-dose insul<br>ple organ sys<br>determined in<br>of this work.<br>In summary **IN SURVER SURVER SURVER SURVER SURVER SURVER SURVER SURVEY AND THE SURVER SURVEY AND THE MANUS WEIGHT AND THE MANUS CONTROLLATION OF SURVEY AND SURVEY AND SURVER SURVEY AND SURVEY AND SURVEY AND LOCAL THE MANUS OF SURVEY** 

ple organ systems on hepatobiliary function must be<br>determined in order to establish the full clinical context<br>of this work.<br>In summary, it is still difficult to explain the many<br>alterations in hepatic uptake, metabolism a determined in order to establish the full clinical context<br>of this work.<br>In summary, it is still difficult to explain the many<br>alterations in hepatic uptake, metabolism and biliary<br>excretion observed in diabetic animals an of this work.<br>In summary, it is still difficult to explain the many<br>alterations in hepatic uptake, metabolism and biliary<br>excretion observed in diabetic animals and humans.<br>Mechanisms that have been suggested include chang In summary, it is still difficult to explain the many<br>alterations in hepatic uptake, metabolism and biliary<br>excretion observed in diabetic animals and humans.<br>Mechanisms that have been suggested include changes<br>in glycogen alterations in hepatic uptake, metabolism and biliary<br>excretion observed in diabetic animals and humans.<br>Mechanisms that have been suggested include changes<br>in glycogen, cyclic adenosine monophosphate (Ackerman<br>and Leibman excretion observed in diabetic animals and human<br>Mechanisms that have been suggested include change<br>in glycogen, cyclic adenosine monophosphate (Ackerma<br>and Leibman, 1977) and growth hormone (Yamazoe e<br>al., 1989a, b) level Mechanisms that have been suggested include changes<br>in glycogen, cyclic adenosine monophosphate (Ackerman<br>and Leibman, 1977) and growth hormone (Yamazoe et<br>al., 1989a, b) levels, ketosis and glucose starvation (Bell-<br>ward in glycogen, cyclic adenosine monophosphate (Ackerman<br>and Leibman, 1977) and growth hormone (Yamazoe et<br>al., 1989a, b) levels, ketosis and glucose starvation (Bell-<br>ward et al., 1988; Hong et al., 1987; Johansson et al.,<br>1 and Leibman, 1977) and growth hormone (Yamazoe et Arwes, M. S., AND HEGNER, D.: Role of inorganic electrolytes in bile acid-<br>al., 1989a, b) levels, ketosis and glucose starvation (Bell-<br>al., 1988, Hong et al., 1987; Johann ward et al., 1988; Hong et al., 1987; Johansson et al., 1986), hyperglycemia and hypoinsulinemia (Marin et al., 1988). In addition, thyroid hormone and insulin may actually function in concert in some areas or as antago-<br>n ward et al., 1988; Hong et al., 1987; Johansson et al., 1986), hyperglycemia and hypoinsulinemia (Marin et al., 1988). In addition, thyroid hormone and insulin may actually function in concert in some areas or as antagonis 1986), hyperglycemia and hypoinsulinemia (Marin et al., 1988). In addition, thyroid hormone and insulin may ARIAN actually function in concert in some areas or as antagonic or monal control of gene expression (Chan et al. al., 1988). In addition, thyroid hormone and insulin may<br>actually function in concert in some areas or as antago-<br>nists analagous to glucagon in other areas of the hor-<br>monal control of gene expression (Chan et al., 1988). actually function in concert in some areas or as antago-<br>mists analagous to glucagon in other areas of the hor-<br>monal control of gene expression (Chan et al., 1988). No<br>single mechanism satisfactorily accounts for all obmists analagous to glucagon in other areas of the<br>monal control of gene expression (Chan et al., 1988<br>single mechanism satisfactorily accounts for al<br>served changes in people with diabetes, however, an<br>unified explanation monal control of gene expression (Chan et al., 1988). No<br>single mechanism satisfactorily accounts for all ob-<br>served changes in people with diabetes, however, and no<br>unified explanation has been proposed. Our understand-<br> expression (Chain et al., 1900). No ARIAS, I. M., AND FORGAC, M.: The sinusoidal domain of the plasma membrane<br>single mechanism satisfactorily accounts for all ob-<br>served changes in people with diabetes, however, and no ch completed.

equivocal at best, and much research remains to be completed.<br> *Acknowledgements*. The authors would like to express their ap-<br>
preciation of the gracious support of the work performed in our<br>
laboratory provided by the In completed.<br>
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laboratory provided by the Indiana Affiliate and the national Amer-Acknowledgements. The authors would like to express their increasion of the gracious support of the work performed in claboratory provided by the Indiana Affiliate and the national American Diabetes Association. Acknowledgements. T<br>preciation of the gracic<br>laboratory provided by t<br>ican Diabetes Associatio

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