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Diabetes Mellitus-Induced Alterations of Hepatobiliary Function

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I. Introduction

Diabetes mellitus may be defined as a commonly occurring disease in which plasma glucose control is defective because of insulin deficiency or decreased target-cell responsiveness to insulin. Diabetes is often accompanied by diverse pathological states, including coronary heart disease, renal insufficiency, cerebrovascular disorders, and neuropathy. Diabetes is also known to produce substantial changes in intracellular metabolism 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 the effects of insulin deficiency on hepatic drug disposition provide evidence that diabetes may also alter the pharmacodynamics and pharmacokinetics of pharmaceutical agents (Watkins and Sanders, 1991), potentially increasing the risk of drug toxicity and side effects or decreasing drug efficacy.

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 Schein, 1963; Twiss and Carter, 1952). Diabetes-induced changes have been observed in biotransformation, both in humans (Daintith et al., 1976; 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; 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 and Dykstra, 1987; Watkins and Noda, 1986; Watkins and Sherman, 1992; Wey et al., 1984).

This paper will present a simplified overview of bile formation, hepatic uptake, and biliary excretion in order to facilitate understanding diabetes-related effects on these functions. Extensive discussions of the general hepatobiliary literature may be found elsewhere (Arias

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† Abbreviations: ATP, adenosine triphosphate; ATPase, adenosine triphosphatase; v_{max}, maximal velocity; UDP, uridine diphosphate.

et al., 1988; Boyer et al., 1992; Coleman and Rahman, 1992; Klaassen and Watkins, 1984; Meijer and Van der Sluijs, 1989; Petzinger et al., 1989a; Siegers and 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 Alloxan-induced Diabetes

Insulin-dependent diabetes mellitus is characterized by low or absent levels of circulating endogenous insulin, and injection of insulin helps control hyperglycemia and ketosis as well as sustain life itself. Although the etiology is unknown, human leukocyte antigen association, viral factors, and various environmental factors may 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 the two hormones function in concert to maintain normal glucose metabolism. In the absence of insulin, there is excess glucagon and a hormonal milieu that favors an increase in hepatic gluconeogenesis and glycogenolysis, a decrease in peripheral glucose uptake, and a decreased conversion of glucose into glycogen. Another pathognomonic 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).

Two experimental models have been extensively used to determine how insulin deficiency may affect hepatobiliary 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; Shafrir, 1990). It has been known for some time that structural alterations in the beta cells of the pancreas occur within 48 h of administration of streptozotocin and 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 (Dixon et al., 1961). Streptozotocin is more specific than alloxan, less likely to cause ketosis, and less prone to interanimal variability in terms of effective dose. Alloxan generally produces greater cytotoxicity owing to its conversion to anionic radicals (Nukatsuka et al., 1989). Pancreatic islet cells treated with alloxan exhibit multiple cellular necrosis, marked degranulation, and extensive vesiculation of the endoplasmic reticulum and Golgi complex, as well as enlarged mitochondria with disrupted cristae and mitochondrial ruptures (Abdel-Rahman et al., 1992). Winkler and Moser (1992) suggest that disruption of the antioxidant tissue defense enzymes is central to the diabetogenic effect of streptozotocin. In fact, superoxide dismutase protects pancreatic islets cells from most of the cytotoxic effects of alloxan, although mitochondria are still enlarged (Abdel-Rahman et al., 1992). Treatment of diabetic rats with vitamin E or probucol alleviates the oxidation of lipoproteins and cytotoxicity without altering hyperglycemia (Morel and Chisolm, 1989).

Interpretation of studies in chemically induced diabetic animals must consider the toxicity of the diabetogenic agents when determining the effect of insulin deficiency. Many studies of diabetic effects have used animals from 1 day to 3 months after treatment with 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; Siegers et al., 1985), as well as on hepatic biotransformation (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 diabetogen rather than diabetes itself. However, many signs of diabetogen toxicity disappear after 14 days, and changes in experimental parameters are probably owing to insulin deficiency itself as addition of exogenous insulin reverses these effects. Future work must unequivocally rule out chronic or delayed toxicity from the diabetogens themselves.

III. Diabetes and Cholesterol Metabolism

Cholesterol, a precursor for plasma membranes, bile salts, steroid hormones, and other molecules, circulates in the plasma as part of various lipoprotein complexes, including chylomicrons, very low density lipoproteins, low density lipoproteins, and high density lipoproteins. Hepatocytes are involved in synthesis and elimination of cholesterol, both through cholesterol degradation into bile acids and through cholesterol secretion into the bile; cholesterol is either reabsorbed from the intestines or excreted in the feces. Hepatic synthesis of cholesterol is controlled homeostatically by the level of dietary cholesterol (Coleman and Rahman, 1992; Turley and Dietschy, 1988).

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 decreased levels of high density lipoprotein cholesterol, along with increased mean plasma concentrations of cholesterol, very low density lipoprotein, low density lipoprotein, triglycerides (Barrett-Connor, 1992; Manzato et al., 1993; Verges, 1991), and apolipoprotein A-I 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 insulin-dependent diabetes and serum concentrations of

lipids and lipoproteins, and two studies have shown 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 and is correlated with plasma triglyceride levels in diabetics (Ahn et al., 1993; Wilson et al., 1993). The lipid content of cell membranes seems to be disrupted by diabetes, as evidenced by increased nonenzymatic glycation, lipid peroxidation, and cholesterol/phospholipid ratio (Watala and Winocour, 1992).

Similar lipid anomalies occur in animal models as well. Tepperman et al. (1983) have shown a reduction in the activity of glycosyltransferases that are involved in membrane glycoprotein synthesis in streptozotocin-diabetic rats. Nonenzymatic glycosylation of proteins is also 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 fractions are enriched with triacylglycerol (O'Meara et al., 1991) and deficient in the major enzymes regulating cholesterol metabolism, hydroxymethylglutaryl-coenzyme A reductase, cholesterol 7α-hydroxylase, and cholesterol acyltransferase (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 well as in platelets, aorta, and adipose cells (Egutkin et al., 1992; Dang et al., 1988).

Hepatic synthesis of cholesterol is increased more than two-fold in diabetic rats fed a high protein diet (Kudchodkar et al., 1988). However, insulin induces a rapid and significant reduction in biliary lipid output in diabetic rats (Villanueva et al., 1990b), suggesting that insulin or its absence may play a role in mechanisms other than synthesis involved in the supply of biliary lipids toward the canaliculi. Insulin deficiency decreases the removal rates of triacylglycerols from the liver as well 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 seems to normalize very low density lipoprotein composition, contributing to the accelerated removal of triglycerides from blood of streptozotocin-diabetic rats (Yoshino et al., 1991). Levels of apolipoprotein E messenger ribonucleic acid are reduced in alloxan diabetic rabbits, suggesting that insulin deficiency influences apolipoprotein E gene expression, thus decreasing hepatic and adrenal cholesterol concentrations (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 regarding diabetes, cholesterol homeostasis, and atherosclerosis appear elsewhere (Schwartz et al., 1992; Staprans et al., 1992; Stern et al., 1992). The functional consequences of streptozotocin-induced diabetes mellitus, with particular reference to the cardiovascular system, were recently reviewed (Tomlinson et al., 1992).

IV. Diabetes and Hepatic Uptake

A. General Considerations Regarding Hepatic Uptake

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 blood plasma is extremely efficient (Aldini et al., 1982). In spite of the very tight binding of most organic anions 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 "surface-mediated dissociation" and the existence of a specific albumin receptor on the sinusoidal plasma 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-organic anion dissociation probably plays a role in hepatic uptake processes in vivo.

As extensively reviewed elsewhere (Berk and Stremmel, 1986; Berk et al., 1987; Kuipers and Vonk, 1991), the hepatic uptake of organic anions such as bilirubin, 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 (Potter et al., 1987) and is accelerated in the presence of chloride (Min et al., 1990; Wolkoff et al., 1987).

Several distinct, class-specific binding proteins in the sinusoidal membrane of the hepatocyte probably represent separate uptake systems for different classes of negatively charged compounds, i.e., for organic anions, bile acids, and fatty acids. For example, a 107 kD protein called bilitranslocase was reported to consist of two nonidentical subunits (α = 37 kD, β = 35.5 kD) with a subunit composition of $\alpha_2\beta$ (Lunazzi et al., 1982). An antibody to bilitranslocase inhibited bilirubin transport in the isolated perfused rat liver and insertion of the protein in liposomes reconstituted sulfobromophthalein transport (Sottocasa et al., 1982). Also, a 55 kD sulfobromophthalein and bilirubin binding protein was isolated from a rat liver plasma membrane fraction enriched in basolateral domains (Stremmel et al., 1983). Monospecific antibodies raised against this protein inhibited the uptake of sulfobromophthalein and bilirubin 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 liver cell plasma membranes (Wolkoff and Chung,

1980) with similar molecular weight and binding characteristics.

At least three different mechanisms are involved in the basolateral uptake of bile acids into rat hepatocytes: (*a*) a Na^+-independent carrier-mediated process, (*b*) a Na^+-dependent bile acid uptake system, and (*c*) nonionic diffusion followed by intracellular binding to cytosolic proteins and amidation with taurine or glycine or conjugation with sulfate or glucuronidate (Meier, 1991; Meier et al., 1984). The saturable, carrier-mediated, Na^+-independent uptake may occur for certain bile acid derivatives including cholate, glycocholate and glycochenodeoxycholate (Van Dyke et al., 1982). More important quantitatively, the electrogenic basolateral Na^+/bile acid cotransport system moves trihydroxy conjugated bile salts such as taurocholate. The hepatocellular Na^+/bile acid uptake system has broad substrate specificity, and possible cosubstrates include steroids and steroid metabolites, cyclic oligopeptides, and numerous drugs. The Na^+/bile acid cotransport system starts to be expressed on the basolateral membrane at late gestation 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., 1988). Na^+-dependent taurocholate uptake has been expressed in *Xenopus laevis* oocytes (Hagenbuch et al., 1990). Finally, the carrier might actually exist as a trimeric or tetrameric aggregate in the plasma membrane, inasmuch as recent radiation inactivation data have suggested a minimal functional molecular mass of the Na^+-coupled bile acid uptake system of 170 kD (Elsner and Ziegler, 1989). Cloning and sequencing of this important hepatocellular bile acid transporting polypeptide is currently in progress in several laboratories.

Finally, undissociated (protonated) unconjugated bile acids are especially prone to diffuse passively across biological membranes. Nonsaturable uptake by nonionic diffusion is definitely relevant for certain hydrophobic bile acids such as ursodeoxycholic and other unconjugated mono- and dihydroxy bile acids (Lake et al., 1988), and may also occur for more water-soluble unconjugated bile acids such as cholic acid (Caflisch et al., 1990).

The isolation of specific binding proteins exhibiting transport functions for organic anions, which differ from those described for bile acids (~48 kD) (Ananthanarayanan et al., 1988) and for fatty acids (~40 kD) (Stremmel et al., 1985), provides evidence that there are separate uptake systems for different classes of negatively 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 et al., 1986; Frimmer and Ziegler, 1988; Meijer et al., 1990; Petzinger et al., 1987; Zimmerli et al., 1989). Further studies are needed to determine whether the Na^+-dependent anion carrier is the 48 kD protein and the Na^+-independent anion system is the 55 kD protein. However, as long as the proteins have not been characterized, one can not exclude the possibility that the sinusoidal membrane contains multiple distinct transport systems with similar molecular weights on sodium dodecylsulfate-gel electrophoresis.

At least two distinct uptake systems transport organic cations and have separate, albeit overlapping, substrate specificities (Neef et al., 1984a,b; Mol and Meijer, 1990; Steen and Meijer, 1991). The monovalent cation carrier is an energy-requiring, Na^+-independent system that is not inhibited by ouabain or taurocholate but strongly blocked by sulfhydryl reagents and choline. Uptake of the more lipophilic bivalent cations is strongly inhibited by ouabain and taurocholate and unaffected by choline. Additional details of the hepatic uptake of organic cations may be found in other reviews (Meijer, 1989; Petzinger et al., 1989a; Stein and Meijer, 1991).

B. Effects of Insulin and Insulin Deficiency on Hepatic Uptake

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. 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, 1974). Enzymes whose activities are affected by insulin treatment or by diabetes include γ-glutamylcysteine synthetase (Lu et al., 1992), tyrosine aminotransferase, γ-cystathionase, cystathionine β-synthase (Hargrove et al., 1989), fructose-1,6-bisphosphatase (Jiminez-Jativa et al., 1992), γ-glutamyltranspeptidase (Vacek et al., 1990; Watkins and Smith, 1993), Na^+-K^+-ATPase (Carnovale et al., 1991) and serine proteinase (Guenet et al., 1989). In addition, hepatic concentrations of insulin-like growth factor-binding protein-1 can be decreased by administration of exogenous insulin and be increased by induction of diabetes in rats with streptozotocin (Ooi et al., 1992).

Lack of insulin in diabetic humans and experimental animals may have pronounced effects on hepatic uptake 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 has yet to be elucidated (Danysz and Wisniewski, 1965; Wisniewski, 1968). Dodeur and coworkers (1982) assert that the diabetes-induced impairment of binding protein is responsible for a 50% decrease in the uptake of asialoorosomucoid by hepatocytes from streptozotocin-diabetic rats. Future studies will need to determine whether or not insulin injection directly affects the synthesis of those transport proteins involved in hepatic uptake.

Diabetes also affects the balance of electrolytes and their transport across hepatic membranes, including

Na^+, K^+, and bicarbonate ions. These disruptions may influence either the uptake (Erlinger, 1982; Scharschmidt et al., 1975) or excretion (Watkins and Noda, 1986) of Na^+-dependent chemicals. Increases in the size of the bile acid pool in diabetic rats may also influence uptake. For example, the disappearance of rose bengal, a bile acid-dependent cholephilic anion, from serum is increased in diabetic rats, as is biliary excretion and bile flow, whereas the serum disappearance of amaranth, a bile acid-independent anion, is unchanged and its biliary excretion inhibited (Watkins and Noda, 1986).

Preliminary studies of taurocholate transport into hepatocytes isolated from normal, diabetic, and insulin-treated diabetic rats indicate that the Km for uptake is unchanged, whereas v_{max} is increased (Schwarz and Watkins, unpublished results). More extensive work in basolateral-enriched and canalicular-enriched hepatocyte plasma membrane vesicles indicates that there is no effect of diabetes on canalicular taurocholate uptake in the presence or absence of ATP. In contrast, a two-fold increase in v_{max} is observed in taurocholate uptake into basolateral-enriched plasma membrane fractions from diabetic rats, whereas uptake into basolateral membranes is similar in preparations from normal and insulin-treated diabetic rats (Watkins et al., unpublished 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 the basolateral surface of the hepatocyte and that insulin treatment normalizes this effect. Additional research is needed to unequivocally demonstrate that diabetes does not alter canalicular membrane transport.

V. Diabetes and Biotransformation

A. Phase I Reactions

Biotransformation is the process, primarily in the liver, by which the body either metabolizes chemicals to pharmacologically or toxicologically active agents or detoxifies endogenous or exogenous compounds and prepares them for elimination. One important component of biotransformation is the microsomal cytochrome P450-dependent mono-oxidase system. The summary in table 1 suggests that there is no consistent evidence that genetic or chemically-induced diabetes alters total cytochrome P450 concentrations in animal models. However, changes in heme content, when they occur, are generally quite small.

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 (table 2) (Past and Cook, 1982; Thomas et al., 1987; Yamazoe 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 isoniazid (Ryan et al., 1985), dimethylsulfoxide and pyrazoles (Thomas et al., 1987), ethanol (Sato et al., 1981; 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 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 P450IIE messenger ribonucleic acid in diabetic rat liver. Although workers

TABLE 1

The effect of diabetes on total hepatic cytochrome P-450 levels

Animal	Diabetes	Male†	Female†	Insulin Reversal	Source
SD* rat	STZ	n.c.			Dong et al., 1988; Faas and Carter, 1980
SD rat	STZ		n.c.		Eacho and Weiner, 1980
SD rat	STZ	↑		yes	Eacho and Weiner, 1980; Favreau et al., 1987; Favreau and Schenkman, 1988a; Reinke et al., 1978
SD rat	STZ		↑	yes	Faas and Carter, 1980; Reinke et al., 1978; Zysset and Tlach, 1987
SD rat	STZ	↓			Watkins and Mangels, 1987; Watkins et al., 1988
SD rat	alloxan	n.c.			Dong et al., 1988
Wistar rat	alloxan	↑			Uchida et al., 1979
Wistar rat	alloxan	n.c.			Toda et al., 1987
Wistar rat	STZ	n.c.			Toda et al., 1987
LE rat	STZ	n.c.			Toda et al., 1987
Holtzmann rat	STZ	n.c.			Ackerman and Leibman, 1977
BB/Wor rat	genetic	↑		yes	Favreau and Schenkman, 1988b
BB/Wor rat	genetic	n.c.			Dong et al., 1988
WKY	genetic	↓			Watkins and Mangels, 1987
mice	genetic	↑	↑		Knodell et al., 1984; Rouer and Leroux, 1980
mice	STZ	↑	↑	yes	Knodell et al., 1984; Rouer and Leroux, 1980
mice	genetic	n.c.			Watkins and Klueber, 1988

* SD, Sprague-Dawley; STZ, streptozotocin; LE, Long Evans, BB/Wor, Wistar, Fisher, Brattleboro; WKY, Holtzmann or Wistar-Kyoto fatty rats or mice (as indicated).

† P450 levels: ↑, increased; ↓ decreased; n.c., no change.

TABLE 2
The effect of diabetes on hepatic cytochrome P-450IIE levels

Animal	Diabetes	Male†	Insulin Reversal	Source
SD* rat	STZ	↑	yes	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	STZ	↑	yes	Thomas et al., 1987
Fisher rat	STZ/alloxan	n.c.		Chawalit et al., 1982
BB/Wor rat	genetic	↑	yes/no	Bellward et al., 1988; Dong et al., 1988; Favreau and Schenkman, 1988b

* SD, Sprague Dawley; LE, Long Evans; BB/Wor, Fisher or Brattleboro rats as indicated.
† P-450 levels: ↑, increased; ↓, decreased; n.c., no change.

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-caused diabetic animals (table 2).

Recent studies on the effects of diabetes on the P450-mediated metabolism of various substrates are summarized in table 3. This heterogeneous group of isozymes has been shown in the rat to be modified by diabetes in a substrate-specific manner. The most studied reactions are aniline hydroxylation and aminopyrine N-demethylation, both of which seem to be dependent on the sex of the animal (Faas and Carter, 1980; Rouer et al., 1982; Skett and Joels, 1985). Induction of diabetes in male rats 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 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 on biotransformation in normal rats. Studies in mice, including genetically diabetic animals, show similar substrate-dependent effects.

Building on these indications that hormonal interactions may play a part in the effects of diabetes, Yamazoe and coworkers (1989b) have demonstrated a relationship 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 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 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 cytochrome P450s that show the sex-related differences in species other than rats and mice. Zysset and Tlach (1986) also suggest that differences in liver blood flow between rats and humans, and therefore hepatic extraction rate 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 I biotransformational capacity of the liver.

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 et al., 1984; Salmela et al., 1980). Daintith and coworkers (1976) find that the plasma half-life of antipyrine 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 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 (Dajani et al., 1974). In the same study, metabolism of phenylbutazone and tolbutamide seems unchanged. Biotransformation of acetophenetidin is also decreased in alloxan-induced diabetic rabbits (Dajani and Kayyali, 1973). Although Redman and Prescott (1973) report no 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 Poffenbarger, 1979; Ueda et al., 1963).

In summary, the numerous alterations in microsomal 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 of cytochrome P450IIE in diabetic animals, more specific studies of the effects of insulin-dependent and insulin-independent diabetes mellitus on hepatic biotransformation in humans are needed. If cytochrome P450IIE is increased consistently in humans, then one could speculate that xenobiotics activated by P450IIE would exert greater toxicity, and those inactivated by P450IIE would be ineffective: a higher dose would be required to acheive therapeutic efficacy. Future efforts need to address this speculation.

B. Phase II Conjugations

Biotransformation also involves the enzymatically mediated conjugation of a xenobiotic with an endogenous water-soluble moiety such as sulfate, glutathione, or glucuronate. The resulting conjugate is usually readily excreted in the urine, bile, or feces.

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-dependent. Diabetes inhibits conjugation of testosterone (Schriefers et al., 1966; Watkins and Klueber, 1988; Watkins and Mangels, 1987; Watkins et al., 1988), 1-naphthol (Grant and Duthie, 1987; Watkins and Klueber, 1988; Watkins and Mangels, 1987; Watkins et al., 1988), phenolphthalein (Grant and Duthie, 1987), salicylic acid (Emudianughe et al., 1988), and 1-aminophenol (Muller-Oerlinghausen 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 1982, 1984), mice (Rouer et al., 1981), rabbits (Hinohara 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 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., 1981, 1982; Tunon et al., 1991; Gonzalez and Fevery, 1992). Morrison and Hawksworth (1982) suggest that variations in glucuronidation of substrates in streptozotocin-treated male rats may be owing to an alteration of the membrane lipid environment, rather than a transferase modification, that might be caused by either streptozotocin or diabetes. Mottino et al. (1991) also postulate that lipid differences at the microenvironment level may explain variations among organs in UDP-glucuronosyltransferase activity.

Diabetes has diverse effects on the glutathione S-transferases as shown in table 5. The activity of glutathione S-transferase toward 1-chloro-2,4-dinitrobenzene 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 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., 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 Mangels, 1987) and mice (Watkins and Klueber, 1988). Conjugation of sulfobromophthalein is decreased in streptozotocin-induced rats (Watkins et al., 1988) but not in genetically diabetic rats (Watkins and Mangels, 1987) or mice (Watkins and Klueber, 1988). γ-Glutamyltranspeptidase activity is dramatically increased in diabetic liver (McLennan et al., 1991; Watkins and Smith, 1993), perhaps as an attempt to conserve glutathione by activation of the hepatic γ-glutamyl cycle.

Other conjugation reactions are also influenced by diabetes. Sulfation of bile acids (Kirkpatrick and Kraft, 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., 1981), which affects many biotransformation reactions. Finally, Toda and coworkers (1987) have observed a decrease in N-acetyltransferase activity in both streptozotocin- and alloxan-treated male rats. In contrast, several studies have been reviewed that indicate the rapid acetylator phenotype is more prevalent among both type 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. Unfortunately, the molecular mechanism for this apparent difference in acetylation has not yet been examined.

Efforts to pinpoint the mechanism of these diabetic effects on phase II biotransformation reactions have shown that in vivo levels of uridine diphosphoglucuronic acid (Hinohara et al., 1974; Schriefers et al., 1966) and 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-glucuronic acid pyrophosphatase and D-glucuronic acid-1-phosphatase (Hinohara et al., 1974) and the concentration of the oxidized form of nicotinamide adenine dinucleotide (Badawy and Evans, 1977) are enhanced. These changes in the conjugation pathway may only begin to explain the diverse effects observed.

VI. Diabetes-induced Changes in Bile Production

A. General Considerations Regarding Bile Formation

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. Aqueous bile is suitable for the excretion of water-soluble compounds and their metabolites. Micelle forming bile acids above their critical micellar concentration allow solubilization of lipid-soluble compounds in bile. Bile also (*a*) assists in fat digestion and absorption by providing bile acids and phospholipids to the duodenum, (*b*) partially neutralizes acidic chyme from the stomach, and (*c*) plays an immunological role by delivering immunoglobulin A to the intestine.

Osmosis is considered to be the major mechanism of water movement during bile formation, although hydrostatic pressure may affect bile formation under experimental and pathological conditions. The osmotic gradi-

TABLE 3

Effects of diabetes on hepatic P-450-mediated metabolic reactions. Animals used are rats unless otherwise noted. Animals are genetically diabetic or treated with streptozotocin (STZ) or alloxan as indicated to induce diabetes

Reaction	Increase	No Change	Decrease
Aniline hydroxylation	*STZ ♂ (Chawalit et al., 1982; Eacho and Weiner, 1980; Faas and Carter, 1980; Favreau et al., 1987; Peng et al., 1983; Reinke et al., 1978, 1979; Thomas et al., 1987; Toda et al., 1987; Warren et al., 1983) #STZ ♂ (Carnovale et al., 1992) *alloxan ♂ (Chawalit et al., 1982; Dixon et al., 1963; Kato et al., 1970; Past and Cook, 1982; Toda et al., 1987) #STZ ♂ mice (Rouer and Leroux, 1980) *STZ ♀ (Faas and Carter, 1980; Reinke et al., 1978, 1979; Warren et al., 1983) alloxan ♂ rabbit (Longhurst et al., 1986) genetic ♂/♀ (Warren et al., 1983)		#STZ ♂ (Ackerman and Leibman, 1977)
Aminopyrine N-demethylation	*STZ ♀ (Faas and Carter, 1980; Reinke et al., 1978; Zysset and Sommer, 1986; Zysset and Tlach, 1987)	*STZ ♂ (Chawalit et al., 1982; Faas and Carter, 1980; Favreau et al., 1987; Reinke et al., 1978; Zysset and Sommer, 1986; Zysset and Tlach, 1987) *alloxan ♂ (Chawalit et al., 1982; Dixon et al., 1963; Hansson, 1989; Toda et al., 1987) genetic BB ♂ (Favreau and Schenkman, 1988a)	
Nitrosodimethylamine demethylation	STZ ♂ (Bellward et al., 1988; Dong et al., 1988; Peng et al., 1983) alloxan ♂ (Bellward et al., 1988; Dong et al., 1988) fasted (Hong et al., 1987) #genetic BB ♂ (Bellward et al., 1988; Dong et al., 1988)		
Ethoxycoumarin O-deethylase	STZ ♂ mice (Rouer and Leroux, 1980) genetic ♂ mice (Reinke et al., 1978)		
Benzphetamine N-demethylation	STZ, genetic ♂ mice (Reinke et al., 1978)	STZ ♂ (Watkins and Mangels, 1987)	STZ ♂ (Peng et al., 1983; Watkins et al., 1988) WKY fatty ♀ (Watkins and Mangels, 1987)
Benzo(a)Pyrene hydroxylation	STZ ♂ mice (Rouer and Leroux, 1980) STZ ♀ (Stohs et al., 1979)	alloxan rabbit ♂ (Longhurst et al., 1986) STZ, genetic ♀ (Warren et al., 1983) genetic ♂ (Warren et al., 1983) STZ ♂ (D'Souza et al., 1988)	STZ ♂ (Peng et al., 1983; Warren et al., 1983) genetic, STZ ♂ mice (Reinke et al., 1978)
Cyclosporin A clearance			
Meperidine demeth.	genetic, STZ ♂/♀ mice (Knodell et al., 1984)		
Pentobarbital hydrox.	genetic, STZ ♂/♀ mice (Knodell et al., 1984)		
Hexobarbital oxidation			*alloxan ♂ (Chawalit et al., 1982; Dixon et al., 1961, 1963) STZ ♂ (Ackerman and Leibman, 1977; Chawalit et al., 1982; Dixon et al., 1961, 1963)

Ethylmorphine N-demethylase	*STZ ♀ (Fass and Carter, 1980)	STZ ♂ (Faas and Carter, 1980; Peng et al., 1983)
Nitroanisole O-demethylase	*STZ ♀ (Eacho and Weiner, 1980)	STZ ♂ (Peng et al., 1983)
	#STZ, genetic ♂ mice (Rouer et al., 1982; Rouer and Leroux, 1980)	
Diazepam 3OH-ase		STZ ♂ (Andrews and Griffiths, 1982, 1984)
Diazepam N-demethylase	STZ ♂ (Andrews and Griffiths, 1982, 1984)	STZ ♂ (Skett and Joels, 1985)
Lignocaine 3OH-ase	STZ ♂/♀ (Skett and Joels, 1985)	
Lignocaine N-deethylase	STZ ♀ (Skett and Joels, 1985)	STZ ♂ (Skett and Joels, 1985)
Imipramine N-oxidase	genetic, STZ ♂ mice (Rouer et al., 1987)	STZ ♂ (Skett and Joels, 1985)
Imipramine N-demethylase		STZ ♂ (Skett and Joels, 1985)
Imipramine 2OH-ase	STZ ♂/♀ (Skett and Joels, 1985)	
Androstenedione	*STZ ♀ (Skett, 1986)	*STZ ♂ (Hussin and Skett, 1988; Skett, 1986)
Styrene oxide hydrolase	genetic mice ♂/♀ (Watkins and Klueber, 1988)	

*, insulin reverses effects; #, insulin has no effect.

ent is provided by organic and inorganic solutes secreted into bile. The interrelationships among different transport processes, metabolic events, and bile formation are incompletely understood. Details of earlier studies can be found in several comprehensive reviews (Anwer, 1991; Arias et al., 1993; Erlinger, 1988; Klaassen and Watkins, 1984; Moseley and Boyer, 1985; Suchy, 1989).

Canalicular bile primarily produced by hepatocytes is secreted into the canalicular space that is surrounded by two hepatocytes and separated from intercellular space by permselective tight junctions (Arias et al., 1993). The location of tight junctions also serves as morphological and functional demarcation points between apical (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 tight junctions that are believed to provide effective barriers against lateral movement of lipids and proteins (Gumbiner, 1987). Tight junctions along with desmosomes and gap-junctions present at the lateral domain are important diffusional barriers between the interstitium and bile. Tight junctions, because of their permselectivity to cations (Bradley and Herz, 1978), provide important selective barriers against reflux of canalicular contents, particularly organic anions. In addition, microfilaments and microtubules in hepatocytes may be involved in canalicular bile formation (Coleman, 1987; Coleman and Rahman, 1992; Erlinger, 1988; Phillips et al., 1986). Bile formed at the canaliculi is modified downstream in the bile ducts (ductular bile) by reabsorption and/or secretion of electrolytes and water.

Active solute transport into canaliculi is primarily responsible for canalicular bile formation (Anwer, 1991; Arias et al., 1993; Meier, 1991; Klaassen and Watkins, 1984). Of all the compounds in bile, bile acids are the most concentrated ones. It is now generally agreed that high concentrations of bile acids in canaliculi provide the major driving force for water movement during bile formation. Canalicular bile flow associated with bile acid secretion is conventionally defined as bile acid-dependent bile flow. However, even in the virtual absence of bile acid, there is a basal bile formation of canalicular origin, commonly referred to as bile acid-independent bile flow, which is estimated from the intercept of the bile flow versus bile acid excretion plot. The slope of the regression line represents bile acid-dependent flow, and is also a measure of the choleretic effect of bile acids (i.e., the increment in bile flow per increment in bile acid excretion). In addition to bile acids, hormones and other compounds also affect canalicular bile formation.

Sodium is the predominant inorganic cation, and Cl^- and HCO_3^- are the major inorganic anions, implicated in the generation of bile acid-independent bile flow (Erlinger, 1988; Klaassen and Watkins, 1984; Moseley and Boyer, 1985; Boyer et al., 1992). Unequivocal evidence in support of specific transport mechanisms responsible for bile acid-independent bile flow is still lacking, and active

TABLE 4

Effects of diabetes on hepatic glucuronidation reactions. All animals are rats unless otherwise noted. Animals are genetically diabetic or treated with streptozotocin (STZ) or alloxan as indicated to induce diabetes

Substrate	Increase	No Change	Decrease
Testosterone			STZ ♂ (Watkins and Mangels, 1987; Watkins et al., 1988) alloxan ♂ (Schriefers et al., 1966) genetic ♂/♀ (Watkins and Mangels, 1987) genetic mice ♂/♀ (Watkins and Klueber, 1988)
1-Naphthol			STZ ♂ (Grant and Duthie, 1987; Watkins and Mangels, 1987, Watkins et al., 1988) genetic ♂/♀ (Watkins and Mangels, 1987) genetic mice ♂/♀ (Watkins and Klueber, 1988)
Phenolphthalein			STZ ♂ (Grant and Duthie, 1987)
Salicylic acid			STZ ♂ (Emudianughe et al., 1988)
1-Aminophenol			alloxan ♀ (Muller-Oerlinghausen et al., 1967)
Diethylstilbestrol		STZ ♂ (Watkins et al., 1988)	genetic mice ♂/♀ (Watkins and Klueber, 1988)
Acetaminophen	STZ ♂ (Price and Jollow, 1982)		
4-Nitrophenol	STZ ♂ (Eacho et al., 1981 a, b) alloxan ♀ rabbit (Hinohara et al., 1974)	STZ ♀ (Eacho et al., 1981b; Hawksworth and Morrison, 1980; Morrison and Hawksworth, 1982)	STZ ♂ (Hawksworth and Morrison, 1980; Morrison and Hawksworth, 1982, 1984) genetic, STZ mice ♂ (Rouer et al., 1981)
Estrone		STZ ♂ (Watkins and Mangels, 1987; Watkins et al., 1988)	
Bilirubin	genetic ♂ mice (Rouer et al., 1982)	STZ ♂ (Carnovale et al., 1987) STZ ♂ mice (Rouer et al., 1982)	genetic/STZ ♂ mice (Rouer et al., 1981)

transport 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). Hepatocytes have a Na^+/H^+ exchanger (Arias and Forgac, 1984; Moseley et al., 1986) and a Na^+-HCO_3^- cotransporter (Renner et al., 1989) on the sinusoidal membrane, and a $Cl^-/HCO_3^-(OH^-)$ exchanger on the canalicular membrane (Meier et al., 1985). These ion transport mechanisms, by regulating intracellular events, may affect biliary excretion of other osmotically active solutes and thereby bile acid-independent flow. Biliary excretion of inorganic ions, in that case, may be mainly owing to solvent drag and diffusion.

A number of organic solutes (bilirubin, glutathione, amino acids) are concentrated in bile in addition to bile acids and could provide the osmotic gradient for bile 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 involved in bile acid-independent flow. Agents that increase or decrease glutathione excretion have similar effects on bile acid-independent bile flow (Ballatori and 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 extrapolated to zero (Ballatori and Truong, 1989). Thus, solutes other than glutathione may also be involved in bile acid-independent bile flow. It is conceivable that the combined osmotic activity of a number of organic solutes excreted into bile contributes to bile acid-independent flow. The contribution of each solute, however, may be apparent only under experimental conditions designed to enhance biliary excretion of that particular solute.

A large number of exogenous organic compounds that are concentrated in bile also increase canalicular bile formation (Klaassen and Watkins, 1984). These compounds can induce choleresis by direct osmotic effects, by increasing biliary HCO_3^- excretion, or by inhibiting reabsorption of electrolytes and fluid from canaliculi (Anwer, 1985; Anwer and Hegner, 1982, 1983a,b). However, future work is needed to define this reabsorptive mechanism.

TABLE 5

Effects of diabetes on hepatic glutathione S-transferase. All animals used are rats unless otherwise noted; animals are genetically diabetic or treated with streptozotocin (STZ) or alloxan as indicated to induce diabetes

Substrate	Increase	No Change	Decrease
1-Chloro-2,4-Dinitrobenzene	STZ mice ♂ (Rouer et al., 1981, 1982) STZ mice ♀ (Agius and Gidari, 1985)	genetic ♂/♀ (Watkins and Mangels, 1987) genetic mice ♂ (Rouer et al., 1981, 1982) STZ ♂ (Carnovale et al., 1992)	alloxan ♂ (Thomas et al., 1989) alloxan ♀ (Muller-Oerlinghausen et al., 1967) STZ ♂ (Aniya et al., 1989; Thomas et al., 1989; Watkins and Mangel, 1987; Watkins et al., 1988; Younes et al., 1980)
Ethacrynic acid			genetic ♂/♀ (Watkins and Mangels, 1987) genetic mice ♂/♀ (Watkins and Klueber, 1988) STZ ♂ (Watkins et al., 1988)
Sulfobromophthalein		genetic ♂/♀ (Watkins and Mangels, 1987) genetic mice ♂/♀ (Watkins and Klueber, 1988)	STX ♂ (Watkins et al., 1988)
1,2-Epoxy-3-(*p*-nitrophenoxy)propane		STZ ♂ (Aniya et al., 1989)	
Dichloronitrobenzene			STZ ♂ (Aniya et al., 1989)

B. Insulin- and Diabetes-induced Alterations in Bile Production and Flow

Insulin acts in numerous ways to promote protein synthesis, regulate enzyme function (either directly or indirectly via glucose or some other metabolic agent), and control carbohydrate metabolism (Porte and Halter, 1981). Moreover, insulin infusion produces a significant choleresis (increased bile flow rate) in normal dogs (Austin et al., 1977; Garberoglio et al., 1983; Jones, 1976; Jones and Meyers, 1979; Snow and Jones, 1978) or rats (Thomsen and Larsen, 1982a,b), apparently by stimulating secretion of sodium and/or bicarbonate ions, thereby influencing bile acid-independent flow (Jones, R. S., et al., 1984). This effect may be secondary to stimulation of sinusoidal Na^+-K^+-ATPase (Thomsen, 1983; Thomsen and Larsen, 1982a; Gelehrter et al., 1984) as well as changes in membrane potential (Wondergem, 1983). Bolus intravenous injections of insulin into normal dogs (Jones and Meyers, 1979) and diabetic rats (Villanueva et al., 1990b) stimulate bile acid excretion and reduce biliary lipid output. How physiological levels of insulin influence hepatic uptake and biliary excretion is poorly understood.

In contrast to administration of insulin, changes in bile flow rates at different times after the onset of diabetes are indicated in table 6. Flow is depressed imme-

TABLE 6

Effect of time after diabetogenesis on bile flow (μl/min/g liver). All animals used are male Wistar or Sprague-Dawley (SD) rats as indicated

Rats	STZ/alx	Time	Anesthetic	Control	Diabetic	% Control	Source
Wistar	STZ	1 day		0.9	0.45	50	Andrews and Griffiths, 1984
Wistar	STZ	1 day	pentobarbital	2.5	1.6	64	Carnovale et al., 1987
Wistar	STZ	1 day	pentobarbital	2.3	1.6	64	Carnovale et al., 1986
Wistar	STZ	1 day	pentobarbital	2.38	1.21	51	Carnovale and Rodriguez-Garay, 1984
		7 day			1.38	58	
		15 day			1.72	72	
Wistar	STZ	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	
Wistar	STZ	4 day	urethane	1.72	1.15	67	Siegers et al., 1979
SD	STZ	21 day	ether	0.87	1.97	236	Kirkpatrick and Kraft, 1984
SD	STZ	30 day	urethane	1.35	1.60	119	Watkins and Dykstra, 1987
SD	STZ	30 day	urethane	1.63	1.60	98	Watkins and Noda, 1986
SD	STZ	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

diately 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 compounds 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 after streptozotocin or alloxan (Uchida et al., 1979; Watkins and Dykstra, 1987; Watkins and Noda, 1986), in spite of the continued presence of hypoinsulinemia and hyperglycemia. In rats treated with nicotinamide, streptozotocin loses its diabetogenic properties but continues to decrease bile flow and bile acid output (Carnovale et al., 1987).

Some workers report bile flow in terms of flow per kg body weight, whereas others report flow per gram liver, resulting in potentially different interpretations of the same data. Because of liver hypertrophy, liver weight/body weight ratios in diabetic rats may be more than 20% higher than in weight-matched controls. Streptozotocin- and alloxan-induced diabetic animals fail to gain weight as fast as normals, leading to even larger differences in the liver weight/body weight ratios of age-matched pairs. Bile flow rates 7, 14, and 30 days after streptozotocin, when calculated in nmol/min/gram liver, 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 85%, 94%, and 130% of normal bile flow, seeming to support the theory that long-term diabetes may have little adverse effect on bile formation.

Decreased bile flow in diabetic rats may be a result of the cholestatic factors hyperglycemia and hypoinsulinemia 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 (Guzelian and Boyer, 1974; Zahavi et al., 1985), apparently at the canalicular level (Munoz et al., 1986). Glucose infusion also leads to decreased secretion of bile acids and electrolytes, such as Na^+, K^+, Cl^-, and HCO_3^-, increased hepatic levels of UDP-glucose and activity of bilirubin glucuronyltransferase, and increased conjugation and biliary excretion of bilirubin (Munoz et al., 1986, 1987). In addition, Olson and Fujimoto (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, hyperosmotic cell swelling stimulates both taurocholate secretion into bile and bile acid-dependent bile flow (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 Garland, 1991), which theoretically could decrease canalicular bile formation. Thus, conflicting effects on bile flow may be obtained when the so-called cholestatic factors of hyperglycemia and intracellular dehydration clash with the choleretic effect of increased bile acid (especially taurocholate) transport. Obviously, future studies must examine these conflicting data on diabetes-induced changes in bile flow rate, as well as address the question of whether or not streptozotocin and alloxan cause long-term delayed toxicity to the liver.

VII. Diabetes and Biliary Excretion

A. General Considerations Regarding Hepatobiliary Excretion

Current knowledge of canalicular membrane transport is derived from three distinct experimental models: the intact liver, isolated liver parenchymal cells, and 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 an experimental model for studies on bile acid secretion, although the intact organ allows only indirect observations of canalicular transport physiology. Direct measurement of canalicular carrier function is accomplished 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 by diabetes-induced alterations in membrane environment, which may affect membrane isolation and purity. These valid concerns, however, should not hinder future efforts to apply this technology to membrane 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 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 offer direct measurements of primary bile contents in the near future.

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 of solute transport by sodium-driven symport and antiport mechanisms, indicate that the liver shares with other epithelia, such as kidney and intestine, common 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. Although the direction of the secretion process is in principle fixed, some compounds can reflux back into hepatocytes (Ballatori et al., 1986; Guzelian and

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 increased in cholestasis. Under those circumstances, canalicular transport proteins may redistribute to basolateral membrane areas, and this sinusoidal secretion may even exceed biliary elimination (Sies, 1989).

Recent reviews of transport studies with canalicular vesicles have suggested that an interplay of primary, secondary, and tertiary transport mechanisms sustain canalicular bile secretion (Arias et al., 1993; Meier, 1988, 1989). Primary transport systems utilize the chemical energy of ATP hydrolysis by ATPases to drive uphill transmembrane solute transport (Arias, 1989; Zimniak 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 likely more 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 transporter (Arias et al. 1993; Zimniak and Awasthi, 1993). P-Glycoproteins, products of the multiple resistance genes, transport mostly hydrophobic, neutral, or positively 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 et al., 1991; Arias et al., 1993; Nishida et al., 1991; Ruetz et al., 1987; Zimniak and Awasthi, 1993). Finally, the nonbile acid carrier can move organic anions across the membrane via either an electrogenic or an ATP-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 glutathione S-conjugates (Kitamura et al., 1990; Kobayashi et al., 1990; Kuipers et al., 1988, 1989). Recent evidence in canalicular vesicles indicates that the canalicular bile acid carrier exhibits a broad substrate specificity and cotransports other monovalent organic anions (Tamai et al., 1990).

Secondary canalicular transport systems use ion gradients coupling substrate transport to parallel or antiparallel ion fluxes or to electrochemical potential differences across the canalicular membrane. A chloride-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 proton extrusion by a Na^+/H^+-antiport (Rothstein, 1989) and sodium-dependent bicarbonate uptake by Na^+-HCO_3^--cotransport (Weintraub and Macken, 1989).

The mechanisms of bile acid traffic into and out of hepatocytes have been reviewed recently (Meier, 1989, 1991). Canalicular membrane transport probably represents 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 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^+-independent (Meier et al., 1984, 1987) where the intracellular negative electrical potential (-30 to 40 mV) 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, microtubule-dependent vesicle-mediated exocytosis seems to play an increasing role in the presence of supraphysiological bile acid loads (Meier, 1991). No one has yet determined how important this exocytosis mechanism is relative to the enlarged bile acid pool in diabetic rodents.

The canalicular bile acid carrier is very likely a 100 to 110 kD protein (Fricker et al., 1987; Hong and Doyle, 1987; Kramer and Schneider, 1989; Ruetz et al., 1987). Polyclonal antibodies raised against this protein inhibit 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 similar molecular weights are present at the canalicular membrane (Margollis et al., 1990; McCaughan et al., 1990). The carrier-mediated secretion is believed to occur by facilitated diffusion down the bile acid electrochemical gradient.

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 and glycine (Ballatori et al., 1986). The secreted reduced glutathione molecule is processed by γ-glutamyltranspeptidase, thereby producing glutamate and the 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 dipeptidylpeptidase IV. Glycine and cysteine also undergo reabsorptive pathways. In contrast, oxidized glutathione and glutathione-drug conjugates do not seem to be split significantly by biliary γ-glutamyltranspeptidase. A natural glutathione conjugate, leukotriene-glutathione (leukotriene C_4), is split by γ-glutamyltranspeptidase, starting the catabolic cascade of the cysteinyl-leukotrienes leukotriene C_4, leukotriene D_4, leukotriene E_4, and leukotriene-N-acetyl-E_4. Leukotrienes are also secreted 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 bilirubin and leukotriene secretion are lacking in transport

mutant rats (Huber et al., 1987). It is as yet unclear whether endotoxins directly affect transport and whether basolateral uptake or canalicular secretion of leukotrienes might be involved in endotoxin action.

In addition to the multi-drug resistance Gp170 carrier protein, the canalicular membrane possesses at least two cation carriers for transporting type I and type II compounds (Steen and Meijer, 1991). Photoaffinity labeling 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 monovalent quaternary amine that was used as a type II model compound reveals two plasma membrane binding polypeptides with apparent molecular weights of 48 kD and 50 kD. Further work to isolate, purify and characterize these putative carriers is needed.

B. Diabetes-induced Alterations of the Biliary Excretion of Endogenous Compounds

Profound alterations in bile composition are observed in insulin-deficient diabetic patients or experimental animals. Very early studies indicate that diabetic patients at autopsy have a greater incidence of gallstones than nondiabetics (Goldstein and Schein, 1963; Lieber, 1952). A large study with 775 diabetic patients versus 1308 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 nondiabetic 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 dietary 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 in 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). Insulin-treated diabetic patients have increased excretion of bile and 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 levels of 12-ketolithocholic acid and cholesterol 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 composition (Andersen et al., 1986, 1988; Ponz de Leon et al., 1978). Meinders and coworkers (1981) postulate that lower intestinal motility, and therefore greater bacterial action, could account for the different concentration of bile acids and thus the observed tendency to gallstones in people with diabetes. Larger epidemiological studies, which control for obesity and hyperlipoproteinemic disorders, are needed to determine whether or not diabetes predisposes patients to cholelithiasis. Most of the available information suggests that the risk of treatment outweighs the potential benefits in most patients with asymptomatic gallstones (Hartford et al., 1990).

Rahman and Coleman (1986) have shown in isolated perfused rat liver that at high bile-acid secretion rates, biliary cholesterol and phospholipid secretion is dependent on that of bile acids. In either alloxan- or streptozotocin-treated rats, the biliary concentration of bile acids, cholesterol, lecithin and phospholipids is markedly increased (Carnovale et al., 1987; Hassan and Subbiah, 1980; Kirkpatrick and Kraft, 1984; Nervi et al., 1974, 1978; Siow et al., 1991; Stohs et al., 1979; Villanueva et al., 1990a; Watkins and Dykstra, 1987; Wey et al., 1984). Serum and liver triacylglycerol concentrations are also 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 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., 1982; Sadahiro et al., 1970), but the composition of the bile acid pool generally shows an increase in taurochenodeoxycholate (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 12α-hydroxylase may explain the increased cholic acid excretion into bile by diabetic rats. Illing (1981) suggests that alterations in bile acid output in streptozotocin-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 intestinal bacteria involved in bile acid biotransformation. It is also possible that the alterations noted in bile acid metabolism may be influenced by the hyperphagia, hypertriglyceridemia, and hypercholesterolemia that accompany the resulting streptozotocin-induced hyperglycemia (Wey et al., 1984; Young et al., 1982).

Nevertheless, the variations in bile composition that 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 (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 infusion of taurocholate seems to be cholestatic and either to inhibit transport (Reichen and Paumgartner, 1979) or to stimulate output of bile acids and cholesterol

(Carnovale et al., 1986; Villanueva et al., 1990a). Biliary excretion of proteins may also be stimulated by taurocholate injection (Marinelli et al., 1988). Taurolithocholate 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 reticulum (Berry et al., 1985). Another study indicates 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-induced diabetic rats, clearance of bilirubin and biliary 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 diabetic rats, and Tunon et al. (1991) find enhanced bilirubin secretion in streptozotocin-diabetic rats. Bile acids clearly influence the hepatic uptake and biliary transport of numerous cholephilic chemicals, but the direction of the influence varies with the cholephil (Klaassen and Watkins, 1984; Strange, 1984).

In addition to bile acids, secretion of several electrolytes (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 potassium and chloride ion concentrations are unchanged from normal (Watkins and Dykstra, 1987). The increase in excretion of bile acids should stimulate bile acid-dependent bile formation, whereas the decrease in bicarbonate 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 formation must also be considered besides the excretion of osmotically active bile acids and inorganic solutes.

All these data indicate that many alterations in the biliary excretion of endogenous compounds occur during periods of insulin administration or insulin-dependent diabetes.

C. Diabetes-induced Alterations of the Biliary Excretion of Xenobiotics

The liver plays a central role in extracting a wide variety of compounds from the portal circulation before their entry into the systemic circulation. In addition to 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 diabetic rats, where there is a qualitative difference in the concentration of the usual metabolites (Jollow et al., 1974; Siegers and Schutt, 1979; Siegers et al., 1983; Watkins and Sherman, 1992). Streptozotocin-diabetic rats are more resistant 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 excreted 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 the bile of diabetic rats, indicating an enhanced breakdown of the glutathione conjugate by γ-glutamyltranspeptidase (Watkins and Sherman, 1992).

Likewise, decreased fecal and biliary levels of metabolites of diazepam are observed in 1-day diabetic rats 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 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 studies have shown that biliary excretion of both digoxin (Watkins and Sherman, 1992) and ouabain (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, uncharged ouabain, and the bile acid taurocholate are enhanced by diabetes, whereas clearance of the bile acid-independent anion phenol red is apparently not affected. Further differentiation indicates that the bile flow rate in diabetics is unchanged by the bile acid-independent organic anions (eosin, amaranth, and phenol-3, 6-dibromphthalein disulfonate) but that certain bile acid-dependent anions (bromcresol green, indocyanine green 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 with nonsteroidal anti-inflammatory properties that is eliminated primarily as ester and ether glucuronides, is cleared more rapidly by streptozotocin-diabetic rats (Lin et al., 1989). It seems from these data that diabetes must affect the activity of various carriers for transport of these chemicals into the bile.

In spite of these published effects of diabetes-induced alterations in the biliary excretion of xenobiotics, there are few epidemiological studies that unequivocally demonstrate that the pharmacodynamics and pharmacokinetics of important drugs are significantly affected. It is not known whether type I insulin-dependent or type II insulin-independent diabetic patients are idiosyncratically hyperresponsive or hyporesponsive to any drug treatment in some fashion that suggests a disease-induced change. Future work must address this concern.

VIII. Effect of Insulin-mimetic Agents on Hepatic Function

Vanadium salts (Nechay, 1984; Nechay et al., 1985; Shechter, 1990), peroxovanadium compounds (Fantus et al., 1989; Leighton et al., 1991), selenite (Ezaki, 1990), molybdate and tungstate (Goto et al., 1992), zinc ion (Shisheva et al., 1992), and chromium (Singh et al., 1992) can all exert insulin-like effects in vitro. Although the mechanism by which vanadate mimics insulin is ill-defined, much data support a theory that vanadate activates glucose metabolism by an insulin-independent mechanism or by skirting the early events of the insulin-dependent cascade (Nechay, 1984; Nechay et al., 1985; Shechter, 1990).

Oral administration of orthovanadate partially normalizes blood glucose concentrations in streptozotocin-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 restores 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 utilization, independently of insulin-receptor kinase activity (Venkatesan et al., 1991). Moreover, oral vanadate therapy over 2 months reduces glycosylated hemoglobin levels, activates glycolysis, and depresses gluconeogenesis 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-diabetic rats (Levy and Bendayan, 1991). These studies provide evidence that dietary orthovanadate can be somewhat effective as an oral agent for treating diabetes.

The first study to examine whether oral orthovanadate therapy normalizes diabetes-induced alterations in hepatobiliary function notes that the increased total and biliary clearances of rose bengal in diabetic rats 4 weeks 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). Finally, bile formation is not reduced, suggesting that the dose of orthovanadate was too low to compromise hepatic perfusion and oxygen consumption. The vanadate-induced reduction in bile flow rate is apparently owing to hypoxia caused by the direct action on vascular smooth muscle resulting in decreased vascular perfusion and not to any inhibition of Na^+-K^+-ATPase (Thomsen and Larsen, 1982b), an enzyme involved in production of the bile acid-independent fraction of bile secretion.

Recent work demonstrates that an alternative biosynthetic pathway of cholic acid via 3α,7α-dihydroxy-5β-cholestane is accelerated by diabetes and that two weeks of oral vanadate treatment partially cancels 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 understood, vanadate does not increase serum insulin concentrations and is not functioning via an insulin-dependent pathway (Ogura et al., 1991).

Unfortunately, all forms of oral vanadate (metavanadate, orthovanadate or vanadyl sulfate) elicit toxicity in 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 insulin-dependent diabetic patients must carefully balance therapeutic versus toxic actions of the agents. The chelator Tiron seems to ameliorate the toxic effects of vanadate and to diminish the accumulation of vanadium in kidney and bone (Domingo et al., 1992).

Moreover, the effect of combined therapies (insulin plus vanadate) on hepatic function has yet to be ascertained. Low-dose vanadate plus insulin therapy may 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 have beneficial effects by reducing oxidative stress in diabetes (Young et al., 1992).

IX. Future Directions

The complexity of both diabetes mellitus as well as hepatic biochemistry and physiology contribute to the difficult task of understanding the effects of insulin deficiency on biotransformation and biliary excretion. Knowing that both alloxan and streptozotocin are cytotoxic, we need to ascertain what, if any, ultrastructural changes occur and how these relate to the observed functional differences. Because many metabolic enzymes whose functions are influenced by diabetes reside in the microsomal fraction, changes in glycogen, cholesterol, and phospholipid levels could influence either transport mechanisms or enzymes bound in the membranes of mitochondria, endoplasmic reticulum, or plasmalemma.

Whereas specific alterations in phase I cytochrome P450 isozymes have been demonstrated, similar studies on the expression of specific phase II isozymes of N-acetyltransferase, the UDP-glucuronosyltransferases, glutathione S-transferases, or sulfotransferases are warranted. No one has yet proven whether restoration of normoglycemia, suppression of glucagon secretion or simply elevation of plasma insulin concentrations is the active factor in the normalization of enzyme activities.

Applicability of short-term and long-term chemically 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-

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 observed a month or more after diabetogen administration are owing to insulin-deficiency and not to a delayed toxic response to the diabetogen. Use of one or several other animal models for both insulin-dependent and insulin-independent diabetes (Shafrir, 1990) might help solve this problem.

Besides laboratory animals, additional work must evaluate drug disposition in diabetic patients. Moreover, 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 cholesterol metabolism with cholelithiasis and gallstones and with atheroma must also be discerned. Finally, studies in chronic diabetics with neuropathy may enable description of problems in hepatobiliary function, deriving from neuropathy, that are superimposed upon initial low-dose insulin effects. Obviously, the impact of multiple organ systems on hepatobiliary function must be determined in order to establish the full clinical context of this work.

In summary, it is still difficult to explain the many alterations in hepatic uptake, metabolism and biliary excretion observed in diabetic animals and humans. Mechanisms that have been suggested include changes in glycogen, cyclic adenosine monophosphate (Ackerman and Leibman, 1977) and growth hormone (Yamazoe et al., 1989a, b) levels, ketosis and glucose starvation (Bellward 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 antagonists analagous to glucagon in other areas of the hormonal control of gene expression (Chan et al., 1988). No single mechanism satisfactorily accounts for all observed changes in people with diabetes, however, and no unified explanation has been proposed. Our understanding of this serious and disabling metabolic disorder is equivocal at best, and much research remains to be completed.

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