Chapter 2

Background Information

Surgery in patients with obstructive jaundice is associated with an increased risk of postoperative acute renal failure and therefore with an increased mortality (Williams et al., 1960). Hepatorenal syndrome is defined as unexplained renal failure occurring in patients with liver disease in the absence of clinical, laboratory or anatomic evidence of other known causes of renal failure. Patients with obstructive jaundice have a tendency to hypotension and to increased susceptibility to hemorrhagic hypotension (Williams et al., 1960; Zollinger and Williams, 1956). Jaundiced animals have shown similar susceptibility to hypotension and uremia (Aarseth et al., 1979; Finberg et al., 1982; Shasha et al., 1976). In chronic bile duct ligation (CBDL) dogs, this is due to a reduction in total peripheral vascular resistance (Shasha et al., 1976). In contrast to the dogs, the conscious rat with CBDL has normal systemic hemodynamics under basal conditions (Better et al., 1980). Despite these normal basal hemodynamics, the CBDL rat model is susceptible to hemorrhagic hypotension (Aarseth et al., 1979; Finberg et al., 1982). This response is attributable to reduce effective blood volume because of splanchnic trapping of blood. This pool is unavailable for defense of the circulation during hemorrhage in the CBDL rat, as well as in the cirrhotic patient (Green et al., 1984). Early reports have stressed on the role of latent hypovolemia in causing hypotension in patients with surgical jaundice (Williams et al., 1960; Zollinger and Williams,

1956). More recent reports have not confirmed hypovolemia in patients with surgical jaundice (Cattel and Brinstingl, 1967).

In jaundiced patients or experimental animals, the kidney may be injured. When the natural excretory route of bile is blocked the kidney becomes the main excretory organ for the retained bile substances. The elimination of bile compound from the body is critically dependent on the kidney.

Physiology of bile and bilirubin

Bile is composed of bile salts, pigments and fats which are kept in micelle forms in an isotonic electrolyte environment. The bile acids are cholic and chenodeoxycholic acids. Some of the acids are conjugated with glycine or taurine to form molecule which are ionized in the alkaline medium of the gallbladder. The hepatobiliary drainage system is the primary route for elimination of the bile products. When this natural system is occluded, bile constituents overflow into the circulation. Under these circumstances, the kidney assumes the major role of eliminating bile products.

Bilirubin is excreted in the urine in patients with conjugated hyperbilirubinemia, but not in normal or in patients with unconjugated hyperbilirubinemia. The excretion of conjugated bilirubin is dependent on the plasma bilirubin, which is not protien bound and thus available for ultrafiltration across the glomerular membrane. In contrast, unconjugated bilirubin is more tightly bound to plasma albumin and is nonultrafiltrable. Urinary excretion of bilirubin occurs predominantly by glomerular filtration (Fulop et al., 1965; Fulop and Brazeau, 1964; Gollan et al., 1978). The bilirubin that appears in the urine is that

portion of filtered conjugated bilirubin that escapes tubular reabsorption. Tubular secretion of bilirubin does not occur.

Hyperbilirubinemia in man ranges from approximately 20 to 30 mg/100 ml during complete occlusion of the common bile duct. However, when renal failure sets in, hyperbilirubinemia may increase to between 70 to 100 mg/100 ml. The plasma concentration of bile acid and salts also undergoes several-fold increases in biliary occlusion from less than 0.01 mg/100 ml to 2-6 mg/100 ml. In obstructive jaundice the daily endogenous load of bilirubin will be balanced by urinary excretion of bilirubin when serum hyperbilirubinemia reaches the level of 25 to 30 mg/100 ml (Fulop et al., 1971). This balance is dangerous. When kidney failure sets in, as often occurs in obstructive jaundice, the major remainery mechanism for eliminating bilirubin is lost. Extreme levels of hyperbilirubinemia may rapidly occur (Fulop 1967; Fulop et al., 1971; Kantrowitz et al., 1967). Conjugated bilirubin has been considered as the factor that sensitizes the kidney to the effects of anoxic damage because normal Sprague-Dawley rats can withstand 60 minutes of renal artery clamping without developing renal failure whereas in CBDL rats, acute renal failure occurs irreversible (Baum et al., 1969; Dawscn, 1964; Dawson, 1968; Dawson and Stirling, 1964). Gunn rats with CBDL that can not form conjugated bilirubin do not develop acute renal failure following 60 minutes of clamping of renal artery (Baum and Stirling, 1969). This comparison shows conjugated bilirubin rather than bile acid as a toxic circulating substance that potentiates the anoxic damage to kidney. Other investigators have formed that infusion of bile acids into normal rats followed by a period of renal ischemia of 30 minutes results in a

reversible form of acute renal failure (Aoyagi and Lowenstein, 1968). Either 30 minutes of ischemia alone or infusion of bile acids alone does not produce kidney failure. Infusion of conjugated bilirubin before the renal ischemia does not result in acute renal failure (Aoyagi and Lowenstein, 1968). These experiments have been shown that it is the bile acid rather than conjugated bilirubin that potentiates ischemic injury to the kidney. Another investigators have focused on the role of endotoxemic in causing renal failure in obstructive jaundice (Bailey, 1976). They think that it is the endotoxemia rather than the retention of bile compounds that predisposes to acute renal failure (Bailey, 1976). Absence of bile salts from the gut as in obstructive jaundice may augment bacterial proliferation and allow absorption of endotoxin from the gut (Bailey, 1976; Kocsar et al., 1969). Furthermore, obstructive jaundice impairs the clearance of endotoxin from the circulation (Aylward et al., 1973; Bailey, 1976). It is not clear how obstructive jaundice or the associated liver damage may lead to these renal changes.

Experiments on animals with obstructive jaundice have yielded interesting results with potential therapeutic implications for patients with obstructive jaundice. There are many experimental models in many different species animals. They are the common bile duct ligation (Better and Massry, 1972), common bile duct ligation and division (Chomdej et al., 1984; Dawson, 1964; Vital, 1982), Choledochocaval shunt (Masumoto and Masuoka, 1980), and infusion of bilirubin or bile via either systemic circulation or intrarenal injection (Alon et al., 1982, Finestone et al., 1984). Two methods are commonly use for interruption of bile flow, ligation of the common

bile duct and section of common bile duct. They lead to jaundice, disturbed liver function and if the procedures sufficiently prolonged, it will lead to the disturbance of the renal system.

Renal Effects of Obstructive Jaundice

In patients with primary biliary cirrhosis, glomerular filtration rate is normal in the presence of jaundice (Chaimowitz et al., 1977). In experimental animals glomerular filtration rate is either reduced (Cattel and Brinstingl, 1964; Hishida et al., 1980; Yarger, 1976), normal (Allison et al., 1978; Better and Massry, 1972; Better et al., 1980) or increased (Levy and Finestone, 1983; Levy and Fechner, 1985).

Effective renal plasma flow is normal in patients with biliary cirrhosis (Chaimowitz et al., 1977). The same as glomerular filtration rate, effective renal blood flow is either reduced (Cattel and Brinstingl, 1964; Hishida et al., 1980), normal (Bloom et al., 1976; Hishida et al., 1982; Better and Massry, 1972) or increased (Allison et al., 1978; Levy and Finestone,1983).

Humans with biliary cirrhosis do not retain salt and water until a relatively late stage of the disease (Chaimowitz et al.,1977). In earlier stages of primary biliary cirrhosis the ability to excrete salt and water load is enhanced (Chaimowitz et al., 1977). This suggests that obstructive jaundice per se does not impair salt excretion and may act as diuretic (Topuzlu and Stahl, 1966). Urinary dilution is normal in patients with primary biliary cirrhosis (Chaimowitz et al., 1977). No systematic study has been reported concerning urinary concentrating ability in obstructive jaundice in

humans. The salt retention and impaired water excretion of CBDL animals appear to be due to hepatocellular damage rather than to retention of bile compounds in the blood. As in cirrhosis of the liver, the mechanism of these renal changes is not clear. It is known, however, that normal liver with intact circulation and biliary drainage is essential for normal homeostasis of sodium. This is supported by the finding that the natriuretic response to saline load in dogs is greater when the infusion is administered into the portal vein than into a systemic vein (Daly et al., 1967). In severe liver disease, associated alterations in renal function include either decreased, normal or increased RBF and GFR.

The mechanisms responsible for the changes in renal function are not clearly understood. The direct stimulus to increase renal vascular resistance is yet unknown. The hypothesis that the sick liver may release or fail to metabolize renal vasoconstrictors is pausible, but no such hepatic vasoconstrictor has yet been identified. Since volume depletion stimulates an autonomic response, it is reasonable to implicate increased catecholamines or renal autonomic nervous activity as causes of renal vasoconstriction in this disease. There is no clear evidence for this hypothesis.

The renin-angiotensin system is chronically activated in patients with cirrhosis. Angiotensin, which is formed within the kidney, has the effects on the renal circulation. It causes renal vasoconstriction and reduced glomerular filtration. However, the renal vasoconstrictor effect of angiotensin is limited by opposing vasodilator mechanisms, especially by prostaglandins produced by the kidney itself. Recent interesting studies suggest the possibility that

the persistent and striking increase in renal vascular resistance might be due to an imbalance between the vasoconstrictor effects of the renin-angiotensin system, which is activated, and the usual counteracting effect of vasodilator, which may be decreased (Levinsky, 1983).

Renal prostaglandins have the capacity to reduce renal vasoconstriction and to preserve RBF and GFR (Dunn and Hood, 1977; Gerber and Nies, 1981). Inhibitors of prostaglandin synthesis, especially the non-steroided anti-inflammatory drugs (NSAIDS) such as indomethacin, have been reported to transiently decrease renal function in patients with diverse type of renal disease (Dunn and Zambraski, 1980). Recent studies suggested that prostaglandin may play a role in the control of renal function and hemodynamics in cirrhosis. Very few studies have been conducted to determine whether renal prostaglandin systhesis, as estimated by prostaglandin excretion or plasma prostaglandin concentration, is elevated in patients with cirrhosis. Some studies have reported elevated plasma prostaglandin concentration (Zusman et al., 1977) and PGE_2 excretion (Zipser et al., 1979; Zipser et al., 1983), whereas others have observed no increase in PG excretion (Wernze et al., 1980) in patients with liver disease. Zambraski and Dunn have recently reported that common bile duct ligation in dogs of 4-12 week duration will increase the urinary PGE_2 excretion rates, and that the administration of indomethacin to such animals will depress both GFR and renal blood flow whereas blood pressure stays constant.

Physiology of prostaglandins

Prostaglandins are a series of fatty acid products derived from the cellular metabolism of arachidonic acid. They found in most and perhaps all mammalian tissues including the kidney. Many investigators have examined the role of prostaglandins in the regulation of renal function. Prostaglandins have been shown to be capable of altering renal blood flow (Bailie et al., 1975; Levenson et al., 1982; Needleman et al., 1974; Owen et al., 1975), glomerular filtration (Levenson et al., 1982), and the urinary excretion of electrolyte and water (Fulgraff et al., 1974; Gross and Bartter, 1973; Johnston et al., 1967; Levenson et al., 1982; Raymond and Lifschitz, 1986; Tannenbaum et al., 1975).

Figure A   Dose-response relationship
between intrarenal prostaglandin
administration and renal blood flow.
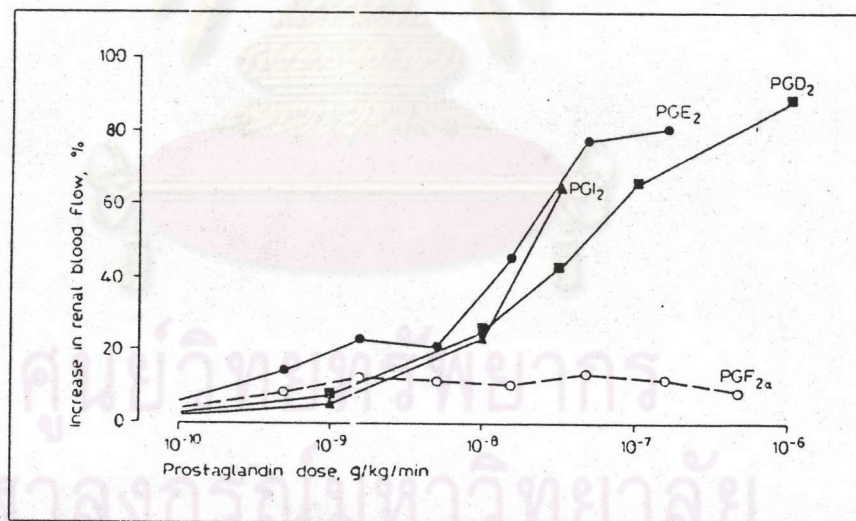
As shown in figure A, early studies in which prostaglandins were infused into the renal artery, usually of dogs, demonstrated dose-related increased in renal blood flow with PGE_2 has virtually no

effect (Gross and Bartter, 1973; Lifschitz, 1981). Once it became possible to measure prostaglandin level in blood, the meaning of these early experiments became somewhat unclear because the concentrations necessary to lead to this kind of change in renal blood flow were rarely if ever demonstrated to exist in vivo. Additional evidence used to support the concentration that prostaglandin in the kidney were normally vasodilator derived from early studies with NSAIDs. When these agents were given to animals under general anesthesia, generally there was a documented decrease in renal blood flow and GFR (Feigen et al., 1976; Lonigro et al., 1973). When subsequent studies were performed in conscious animals under normal physiological conditions, similar doses of NSAIDs led to no documented change in renal blood flow or GFR (Swain et al., 1975; Zins, 1975). More recently it has been considered that the prostaglandins may play no important hemodynamic physiological role by themselves, but rather they may act to modulate the vasoconstricting effects of hormones such as angiotensin II, norepinephrin and vasopressin (Dibona, 1986). A variety of studies have demonstrated increased in systemic or renal vascular resistance when these vasoconstricting compounds are given following inhibition of prostaglandin synthesis with NSAIDs (Dibona, 1986). Therefore, under basal conditions, the endogenous prostaglandins may not play an important role in regulating renal hemodynamics, but that when vasoconstricting hormones are present, the endogenous prostaglandins act to modulate their effects and also limit the decrease in renal blood flow and GFR that might otherwise occur.

Some of the earliest studies in which the effects of prostaglandins on salt excretion were characterized were performed by

infusing these compounds either into the aorta close to the renal artery or directly into the renal artery itself. Both PGE_2 and PGI_2 were found to be natriuretic and diuretic agents (Bolger et al., 1978; Johnston et al., 1967). The ability of PGD_2 to increase salt excretion was quite limited (Bolger et al., 1977). $PGF_{2\alpha}$ was without effects (Gross and Bartter, 1973). In all of these early studies, it was unclear whether the diuretic effects of prostaglandins were the result of their hemodynamic consequences or some more direct tubular inhibitory action (Hart and Lifschitz, 1987).

Prostaglandins have been shown to moderate water transport in several vasopressin-sensitive epithelial cell systems. The exact mechanism by which this occurs is not fully explained. However, considerable investigation over the past several years has resulted in a much better understanding of the cellular events involved in this process.

Indomethacin, because of its potency as an inhibitor of prostaglandin biosynthesis in vivo (Flower, 1974), is widely employed as a pharmacologic agent to investigate the renal actions of endogenous prostaglandins. Evidence for inhibition of renal prostaglandin production in vivo has usually been established by demonstrating a reduction of prostaglandin release, i.e., a lowering of prostaglandin concentration in renal venous blood or a decreased urinary excretion of prostaglandins (Roman et al., 1978).