Chapter 5

Discussion

Five days after bile duct ligation, plasma total and direct bilirubin level increased (Table I and Figure 1). This findings are similar to previous studies (Trams and Symeonidis, 1957; Masumoto and Masuoka, 1980). Trams and Symeonidis (1957) ligated the common bile duct of male Osborn-Mendel rats and found that over a period of 2 to 7 days following ligation of the bile duct, the animals showed a marked increase in serum bilirubin. This markedly increase in total serum bilirubin was also reported by Masumoto and Masuoka (1980) who found that total serum bilirubin increased from 0.3 ± 0.2 mg/dl to 6.4 ± 4.1 mg/dl after 3 weeks bile duct ligation in dogs. It was shown that obstructive jaundice could be produced by ligating the common bile duct in experimental animals.

In the present study, after biliary obstruction, there were no alterations in mean arterial blood pressure, heart rate and hematocrit. These findings are consistent with the previous studies (Better et al., 1980; Hishida et al., 1982; Shasha et al., 1976). In dog, systemic and renal hemodynamic studies were performed in 5 days before and 5 weeks after bile-duct ligation. After the operation there was an insignificant change in mean arterial pressure. It was concluded that renal failure of the dog with bile-duct ligation was not attributed to heart failure (Shasha et al., 1976). In the rat and rabbit with bile-duct ligation, diminished total renal blood flow occured, although no significant difference was found in hematocrit

and blood pressure between the bile duct ligation and the control group (Better et al., 1980, Hishida et al., 1982). These investigations were contradicted to that found in humans (Williams et al., 1960). This group of investigators found that in 350 patients with surgical jaundice, hypotension followed by uremia was the most common complication which led to death. A systolic blood pressure below 90 mmHg for two hours or longer usually caused a rise in the blood urea nitrogen. Furthermore, studies in dogs confirmed the clinical suspicion that the kidneys in the presence of obstructive jaundice were more sensitive to hypotension (Melman, 1978). The occurance of hypotension was due to a decrease in peripheral vascular resistance, but cardiac output was increased in the dog with common bile duct ligation (Shasha et al., 1975). In rats, after bile duct ligation plasma volumes were found to be reduced and hematocrit slightly increased. However, mean arterial blood pressure was not decreased (Yarger, 1976).

In the present experiment, after 5 days of biliary obstruction, RBF and GFR were found to be greatly increased to about 62% and 52% of control group, respectively (Figures 8,4). Our findings seem contradict to the studies reported in dogs with chronic ligation of the bile duct. There were no changes in glomerular filtration rate and renal plasma flow (Better and Massry, 1972). However, in spite of normal systemic hemodynamics, in the conscious chronically bile-duct-ligation rat, total renal vascular resistence increased greater than twofold, whereas total renal blood flow decreased more than 40% of the control (Better et al., 1980). Yarger (1976) concluded that the whole-kidney glomerular filtration rate and

plasma flows were reduced to 59% and 57% of control values respectively. Several investigators believed that renal vasoconstriction occured in the experimental animals with chronic ligation of the bile duct. It might be due to an imbalance between the vasoconstriction effects of the renin-angiotensin system, which is activated, and the usual counteracting effect of vasodilator mechanisms, which may be decreased. However, urinary prostaglandin excretion was found to be increased in cirrhosis (Zipser et al., 1979). If these patients were treated with prostaglandin blockers, there was a striking reduction in creatinine clearance and sodium excretion. However, Zambraski and Dunn group (1984) was the first to examine prostaglandin excretory rates in the animal model of liver disease. They demonstrated the significant increases in prostaglandin E_2, prostaglandin $F_{2\alpha}$ and 6-keto-prostaglandin $F_{1\alpha}$ excretion rates after chronic ligation of the bile duct, by approximatedly 100, 80 and 500 percent, respectively. Levy et al (1983) studied in dogs with chronic ligation of the bile duct and documented significant reductions in glomerular filtration rate and renal plasma flow after administration of indomethacin (2mg/kg). These data demonstrated that, in dogs with experimental liver disease produced by chronic bile duct ligation, renal prostaglandin synthesis was increased. They suggested that the enhanced synthesis of vasodilatory prostaglandins served to maintain renal blood flow and glomerular filtration rate.

In some studies, renal blood flow increased acutely after bile duct ligation. In anesthetized dogs before and 4 hour after the acute obstruction of the common bile duct (ABDL), renal hemodynamics was not associated with any change in systemic hemodynamics (Levy and

Finestone, 1983). There were increases in glomerualar filtration rate by 15.3%, effective renal plasma flow by 13.3% and renal blood flow by 13%. The increment in renal perfusion was maintained for 2-3 days before returning to the baseline level. Levy and Fechner (1985) demonstrated that 4 hour post-acute bile duct ligation, there was a significant increase in renal perfusion and GFR which might last for 2-3 days before returning to the baseline levels. They infused ∝-adrenergic and angiotensin blockers in their study and concluded that the return to baseline was due to the disappearance of a vasodilator effect, although the mediator at the moment remains unknown. So, in this study, after 5-day biliary obstruction in rats, renal blood flow and glomerular filtration rate were increased. However such increase in renal hemodynamic tended to be transient rather than sustained (In our preliminary study indicated that, after 2 and 10 days of biliary obstructed rats the RBF and GFR values were not significantly different from sham control rats). After infusion of indomethacin, an inhibitor of prostaglandin production, to the rats with biliary obstruction, renal blood flow and glomerualr filtration rate were reduced back to the control level. In contrast, indomethacin had no effect when it was given to sham control rats (Table III, Figures 3,5,7). These results agree with the clinical finding of other investigators (Levy et al., 1983). They measured inulin and PAH clearance before and after the intravenous administration of 2 mg/kg indomethacin. The levels of inulin and PAH clearance declined by 42% and 43%, respectively. They interpreted that severe cirrhosis of the liver activated the renin-angiotensin system so as to stimulate renal prostaglandin synthesis, and the resultant vasodilatory effect of

renal prostaglandins tended to restore renal vascular resistance and hence renal perfusion toward normal. The absence of the effect of indomethacin on RBF and GFR in sham control animals agreed with the result reported by Swain et al (1975) and by Zins (1980), who observed no change in renal hemodynamics in anesthetized, sodium replete animals. Our experimental results are consistent with the clinical findings of Zipser et al (1979), who found that indomethacin or ibuprofen reversibly decreased creatinine clearance by approximately 50% in 12 patients with alcoholic cirrhosis. The decrease in para-amino hippuric acid and creatinine clearance in cirrhotic patients given indomethacin was also reported (Boyer et al., 1979).

The present work demonstrated that the renal handling of salt and water was well maintained in the stage of 5 days biliary obstruction (Tables V,VI,VII, Figures 15-25) . There seems to exist a controversy concerning the renal handling of salt and water in obstructive jaundice (Allison et al., 1978; Bank and Aynedjian, 1975; Better and Massry, 1972; Gliedman et al., 1970; Hishida et al., 1982; Yarger, 1976). The natriuretic response to saline load is blunted in bile duct ligation dogs, though sodium clearance in the control state was not different from that in normal dogs (Gliedman et al., 1970). Better and Massry (1972) demonstrated the enhanced renal sodium reabsorption and impaired excretion of a water load in jaundiced dogs 2-7 weeks after the ligation of the biliary tract. Furthermore, the rat models showed sodium retention with massive ascites 4-14 days after bile duct ligation, in spite of no histological change in the liver (Yarger, 1976; Bank and Agnedjian, 1975). In contrast to these findings, there was no sodium retention in jaundiced rats 3 week

after bile duct ligation (Allison et al., 1978). The renal handling of salt and water was well maintained even during saline loading. Also, ascites was not detectable and histological observations revealed no cirrhotic changes in the liver 10 days after the ligation of the biliary tract (Hishida et al., 1982). However, there was a rise in GFR, RBF, urine flow and sodium excretion in 4 hour of acute biliary obstruction dogs (Levy and Finestone, 1983). It was belived that the rise in GFR and RBF associated with acute bile duct ligation did not explain the observed natriuresis, because in several dogs which acute bile duct ligation failed to increase GFR or renal perfusion, sodium excretion still increased significantly, furthermore in some dogs which GFR and RBF increased, whereas sodium excretion did not. When the acute bile duct ligation was relieved, GFR and sodium excretion declined at different rates, with the latter variable returning to the base-line levels while GFR remained elevated. It was postulated that at least two separate factors might be involved, one influencing the microcirculation and the other acting on the tubular transport of sodium, since the rise in GFR and sodium excretion could be dissociated temporarily and one change could occur without the other.

From this experimental data renal handling of salt and water after given vehicle (bicarbonate solution) and indomethacin solution, were increased significantly when compared with control and the pretreatment period of biliary obstructed rat (without given vehicle or indomethacin solution) (Tables V,VI,VII and Figures 15-25). These alterations may be primarily due to the vehicle. Also bicarbonate solution administration will raise the plasma HCO_3 concentration. The normal response to an increase in the plasma HCO_3 concentration is to

excrete the excess HCO_3 in the urine. However, the reabsorption of HCO_3 is linked to Na^+ transport. The infusion of $NaHCO_3$ expands the extracellular volume, a stimulus known to diminish proximal Na^+ reabsorption. So extra Na^+ would be excreted in the urine (Rose,1984). When Na^+ is excreted in the urine, they will also pull water and other ions to be excreted in the urine. However, the data of renal handling of salt and water in the groups which infused vehicle and indomethacin were not different significantly. Then, it may be concluded that indomethacin did not affected the renal handling of salt and water, but the data were changed because of the vehicle (bicarbonate solution).

In summary, this experiment demonstrated that after 5 days of biliary obstruction in rats there were significant increases in GFR and RBF but other parameters showed the pattern similar to that observed in control group. However, GFR and RBF were decreased almost equal the control following indomethacin infusion. At least prostaglandins which are inhibited by indomethacin may be associated with a rise in GFR and RBF. Thus, prostaglandin may play an important role in regulating renal hemodynamics in rats after 5 days of biliary obstruction.