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NEPHROLOGY FORUM

Renal and cardiovascular dysfunction in liver disease

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Case presentation

A 46-year-old mother of two was first admitted to the Rambam Hospital 14 years ago because of severe itching. For the 11 years prior to that admission, she had experienced generalized itching, dry mouth and eyes, and episodic jaundice with dark urine and light stools. On physical examination she was well nourished and had a blood pressure of 140/90 mm Hg. Her skin had an olive hue and revealed many new and old scratch marks. The lower edge of the liver was palpated 3 cm below and that of the spleen 2 cm below the costal margin. Laboratory studies were unremarkable except for a total bilirubin of 1.6 mg/dl and an alkaline phosphatase 2.5 times the upper limit of normal. Administration of cholestyramine, 4 g/day, produced relief from the itching. Intravenous cholangiography and intravenous pyelography were normal. For the following nine years, her condition was stable except for recurrent jaundice.

She was hospitalized again 5 years ago. Physical examination revealed mild jaundice and clubbing of the fingers. The blood pressure was 130/90 mm Hg. The liver and the spleen were palpable 14 cm and 4 cm below the costal margin, respectively. Endoscopy revealed esophageal varices. Total serum bilirubin was 3.7 mg/dl (60% conjugated); alkaline phosphatase, three times the upper limit of normal; and serum glutamic oxaloacetic transaminase, 54 U (normal, below 40 U). Serum albumin was 4.1 g/dl and globulin 2.7 g/dl. Tests for anti-smooth muscle and antimitochondrial antibodies were positive. Antinuclear factor also was strongly positive. Serum IgM was 250 mg/dl (normal, below 180 mg/dl); IgG, 235 mg/dl (normal, below 146 mg/dl); and IgA, 515 mg/dl (normal, below 420 mg/dl). A liver biopsy at that time showed distortion of the normal lobular architecture with formation of micronodules. The portal spaces were fibrotic and heavily infiltrated with lymphocytes together with some plasma cells and eosinophils. The inflammatory infiltrate invaded the lobules causing piecemeal necrosis of liver cells. There were signs of cholestasis within the distorted bile ducts, and bile pigments were found in the liver cells. Orcein staining gave a positive reaction for copper in moderate amounts. These findings were considered compatible with advanced primary biliary cirrhosis.

Two years ago peripheral edema and ascites appeared for the first time. The blood pressure was 110/60 mm Hg and the total serum bilirubin was 6.7 mg/dl (60% conjugated). Serum albumin was 2.5 g/dl and serum globulin was 4.5 g/dl. Serum creatinine was 0.9 mg/dl and serum calcium 8.2 mg/dl. Spironolactone and furosemide produced a diuresis with marked improvement in the edema and ascites. Vitamins A, D, K, and B complex also were given. A few months later she developed hepatic encephalopathy, and treatment with lactulose and oral neomycin was started. One year ago her ascites became increasingly resistant to combined treatment with bed rest, a salt-poor diet, and diuretics. The use of a Le Veen shunt was considered but had to be postponed.

She was readmitted six months ago because of anasarca and deep coma. The blood pressure was 100/60 mm Hg. Anemia and pancytopenia were present and the prothrombin time was grossly prolonged. Total bilirubin was 5.3 mg/dl and the SGOT was 65 U. Serum sodium was 119 mEq/liter; potassium, 4.1 mEq/liter; bicarbonate, 18 mEq/liter; chloride, 85 mEq/liter; osmolality, 260 mOsm/kg; BUN, 30 mg/dl; creatinine, 3.5 mg/dl; and albumin, 1.5 g/dl. The 24-hr urine volume was 350 ml with an osmolality of 400 mOsm/kg and a sodium concentration of 5 mEq/liter. Several days after admission she died following a massive gastrointestinal hemorrhage. Her clinical course is depicted in Figure 1.

Discussion

DR. ORI S. BETTER (*Chief, Department of Nephrology, Rambam Hospital; Annie Chutick Professor of Medicine, and Member, Rappaport Family Institute for Research in the Medical Sciences, Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel*): The patient under discussion had primary biliary cirrhosis (PBC) proved by liver biopsy with characteristic cholestatic jaundice and serologic and immunologic abnormalities. The beginning of the disease with sicca syndrome and itching in a woman in the fifth decade, and the protracted phase of benign cholestasis are typical for this disease. Severe complications secondary to advanced cirrhosis began to appear more than 20 years after the onset of the first clinical manifestations of the disease. Among them were portal hypertension 5 years ago and, 3 years later, edema, ascites, and hepatic encephalopathy. The edema and ascites initially responded to conventional therapy but after one year became increasingly refractory to treatment. On her final admission 25 years after the apparent onset of the disease, she developed arterial hypotension and the hepatorenal syndrome. The terminal event was a massive gastrointestinal hemorrhage.

The disease course in this patient allows us to discuss some

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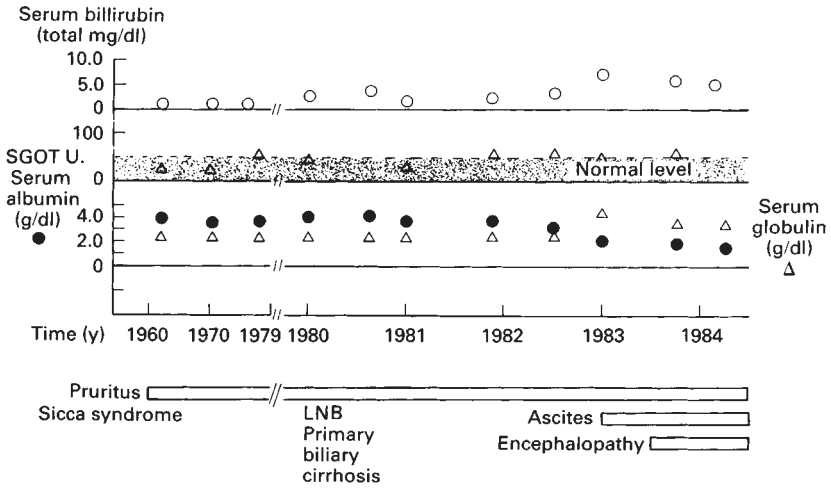

Fig. 1. *Clinical course of the patient under discussion.* Not shown here are levels of blood alkaline phosphatase that were elevated between two and three times the upper normal range throughout the course. The blood pressure between 1960 and 1982 was 140/90 mm Hg and showed a tendency to decline after 1982. In the final admission, blood pressure was 100/60 mm Hg. During this admission she developed the hepatorenal syndrome and died of massive gastrointestinal hemorrhage.

aspects of the disturbed volume regulation in cholemia and in cirrhosis, two common conditions that predispose patients to renal failure. Renal involvement in advanced liver disease was discussed in two previous Nephrology Forums [1, 2] and in an editorial in *Kidney International* [3]. I therefore will focus this discussion on the effects of chronic liver disease and cholestasis on the kidney and on the circulation, effects that have not yet received adequate attention. The main questions I will address here are: (*1*) Why are edema and ascites such *late* complications in patients with PBC? (*2*) Is bile per se nephrotoxic? (*3*) What role does cardiovascular dysfunction play in the severe renal insufficiency that complicates advanced chronic liver disease?

Salt retention in primary biliary cirrhosis

In contrast to Laennec's cirrhosis, in which edema and ascites occur even in moderately advanced stages of the disease, salt retention is a late complication in PBC [4, 5]. There are several explanations. Because PBC progresses slowly and causes predominantly cholestasis rather than parenchymal liver damage, liver architecture and metabolic functions remain spared for many years. The major causes of disturbed volume homeostasis such as hypoalbuminemia and portal hypertension are late complications. As I noted before, edema and ascites developed in this patient more than 20 years after the onset of the disease, only when hypoalbuminemia appeared. Although portal hypertension was present for at least 3 years, it alone did not cause sodium and water retention. We believe that factors independent of prolonged preservation of normal liver function keep the patient with PBC free of edema until late in the disease. Studies from our laboratory show that when patients with PBC are challenged with a standardized intravenous volume load, they exhibit an exaggerated natriuretic response, the mean of which is twofold greater ($P < 0.001$) than that in normal subjects [6]. By contrast, patients with compensated Laennec's cirrhosis have a blunted natriuretic response to such a volume challenge. Simultaneous investigation of renal handling of phosphate and free water formation suggests that the site of the exaggerated natriuretic response to volume expansion in PBC occurs proximal to the diluting segment [6]. These observations have prompted us to suggest that a natriuretic factor contributes to keeping patients with PBC free of edema until the disease reaches an advanced stage. When we first made these observations in 1977, we were not aware of any explanation for the exaggerated natriuresis in PBC. However, we now know that the liver is a prerequisite for normal natriuresis. Vascular exclusion of the liver in the dog [7] and partial hepatectomy in the rat [8] abolish the normal natriuretic response to volume expansion. These findings, and the observation that intraportal infusion of saline causes greater natriuresis than does systemic intravenous infusion, raised the hypothesis that the liver contains sodium receptors and that it elaborates a natriuretic factor (reviewed in [9]). Such sensory function of the liver is teleologically advantageous. The liver is the first organ to "see" changes in portal blood tonicity following a meal or ingestion of water. Theoretically, increased production of hepatic natriuretic factor in primary biliary cirrhosis could account for the supranormal natriuretic response. Nonetheless, we have no basis for such an assumption. Other mechanisms might well be operative.

We have proposed that pronounced renal effects of high plasma concentrations of bile can explain both the exaggerated natriuresis in PBC and the lack of salt and water retention until late stages of the disease. The striking destruction of the bile ducts in PBC causes cholestasis with retention of bile constituents in the circulation. Bile has a natriuretic effect when injected intravenously in the dog [10]. These studies were extended by Alon et al in our laboratory [11] (see Figs. 2 and 3). We showed that intrarenal infusion of dilute bile caused a pronounced natriuresis without affecting GFR or renal plasma flow. Further studies showed that bile salts rather than bilirubin were responsible for the natriuretic action of bile [11]. Even more striking were the observations by Levy and Finestone, who showed that acute (4-hour) obstruction of the common bile duct in the dog caused not only pronounced natriuresis but also a significant increase in GFR and renal plasma flow [12]. They confirmed our findings that bile salts were the compounds responsible for the natriuresis [13]. Moreover, intrarenal infusion of bile salts in the dog was not followed by an increase in GFR and renal plasma flow [11, 13]. Therefore, the hepatobiliary factor that increases GFR and renal plasma flow during acute biliary obstruction in the dog remains elusive. Thus retention of bile salts during acute cholestasis apparently aug-

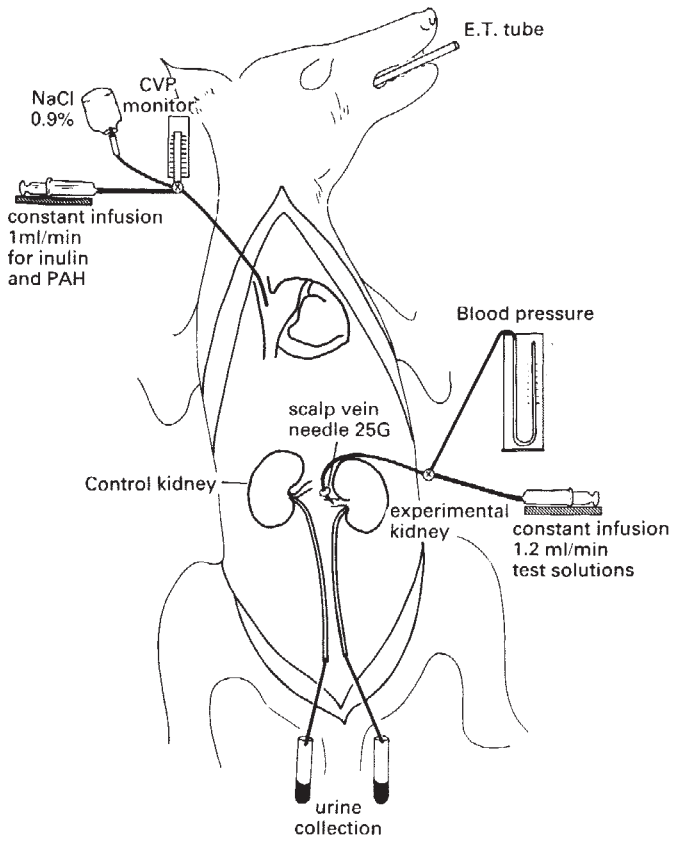

Fig. 2. *Diagrammatic sketch of the experimental procedure of intrarenal bile infusion in the dog.* Bile is infused intrarenally into the experimental kidney. Urine is collected individually from each kidney. The contralateral kidney serves as control. Inulin and PAH clearances as well as central venous pressure and arterial pressure are monitored. (Adapted from [11].)

ments natriuresis. We propose that an increase in circulating bile salts promotes natriuresis in PBC and that this natriuretic effect might contribute to the long delay in the appearance of edema and ascites. In acute biliary obstruction, retained bile salts might produce renal sodium wasting and volume depletion, thus aggravating other common volume losses caused by vomiting, diarrhea, and insensible water loss due to fever. Circulating bile salts thus might contribute to hypovolemia and to a type of "prerenal" azotemia.

Is bile nephrotoxic?

Several investigators have noted that patients with obstructive jaundice have an increased risk of postoperative renal failure [14–17]. Moreover, the greater the degree of preoperative hyperbilirubinemia, the greater the risk of renal failure [14]. In experiments with rats subjected to bile duct ligation, Baum, Sterling, and Dawson suggested that conjugated hyperbilirubinemia sensitized the kidneys to anoxic damage [18]. In contrast, Aoyagi and Lowenstein proposed that bile salts rather than bilirubin aggravate the ischemic damage in the rat kidney [19]. Our studies and those of Levy et al clearly show that in the normal dog direct intrarenal infusion of bile in dilutions greater than 1:10 and at a rate of 1 ml/min does not impair GFR or renal plasma flow [11–13] (see also Figs. 2 and 3). Moreover, acute bile duct ligation actually increases GFR and renal blood flow in the dog [12]. Preliminary studies in our laboratory showed that intrarenal infusion of dilute bile into the dog increased renal production of prostaglandin E_2 (PGE_2). Furthermore, indomethacin abolished both the natriuresis and the increase in renal PGE_2 synthesis associated with intrarenal infusion of bile (Alon U, Davidai G, Berant M, Mordechovitz D, Better OS, unpublished observations).

All these experiments suggest that moderate cholemia is not nephrotoxic. This may partly answer the question raised by Papper: does jaundice contribute to precipitation of the hepatorenal syndrome (HRS)? In Papper's extensive personal series of 200 patients with HRS, progressive jaundice preceded the occurrence of HRS in 40% of the patients [20]. Our results in the dog suggest that increasing jaundice as a prelude to the HRS in humans is a marker of deteriorating liver function but that high bilirubin concentrations are not nephrotoxic.

Cardiovascular dysfunction in liver disease

After 23 years of illness, the patient we are discussing here began to be hypotensive (blood pressure, 110/60 mm Hg versus 140/90 mm Hg in previous years). What was the reason for this lowering of arterial blood pressure? There are multiple causes of hypotension in chronic liver disease (Table 1) [3]. In addition to maldistribution of blood, interstitial fluid, and hepatic lymph, a disturbance within the blood vessels themselves renders them resistant to vasoactive agents. This inherent vascular dysfunction can be observed not only in vivo [21–23] (see also Fig. 4), but also in vitro in isolated arteries, veins, and vasa deferentia taken from animals subjected to chronic bile duct ligation [24, 25]. The reason for this resistance to pressor agents has not been clarified. It can be mimicked by the addition of dilute bile or bile acids to the in-vitro perfusates of these blood vessel preparations [24]. Blunting of the pressor response is achieved in the isolated portal vein of the rat with bile acids in micromolar concentrations [24]. Concentrations of circulating bile acids of this magnitude occur in obstructive jaundice in humans. The portal vein might be sensitive to such a low concentration of bile acids because of its unique exposure to bile acids that are absorbed from the gut. I conclude that bile acids, in addition to their influence on volume, might contribute to vasodilation and induce hypotension.

Myocardial dysfunction also can be a major contributor to hypotension in liver disease. Diminished venous return due to tense ascites [26], alcoholic myopathy, and malnutrition all can interfere with myocardial performance. Gould et al carried out cardiac catheterization in 10 patients with cirrhosis who had a presystolic gallop [27]. When exercising, all 10 patients showed an average increase in left ventricular end-diastolic pressure from 6.0 to 19.0 mm Hg (an increase of 216%). A striking increase also was noted in pulmonary artery pressure (24 to 47 mm Hg; +96%). This observation, coupled with the finding that correction of the hypotension with vasopressors may precipitate pulmonary edema in patients with cirrhosis (28), suggests that some patients with cirrhosis have latent congestive heart failure that is ameliorated by the decrease in afterload brought about by peripheral vasodilation. In these two clinical studies [27, 28], however, the contribution of chronic alcoholism to myocardial dysfunction cannot be excluded.

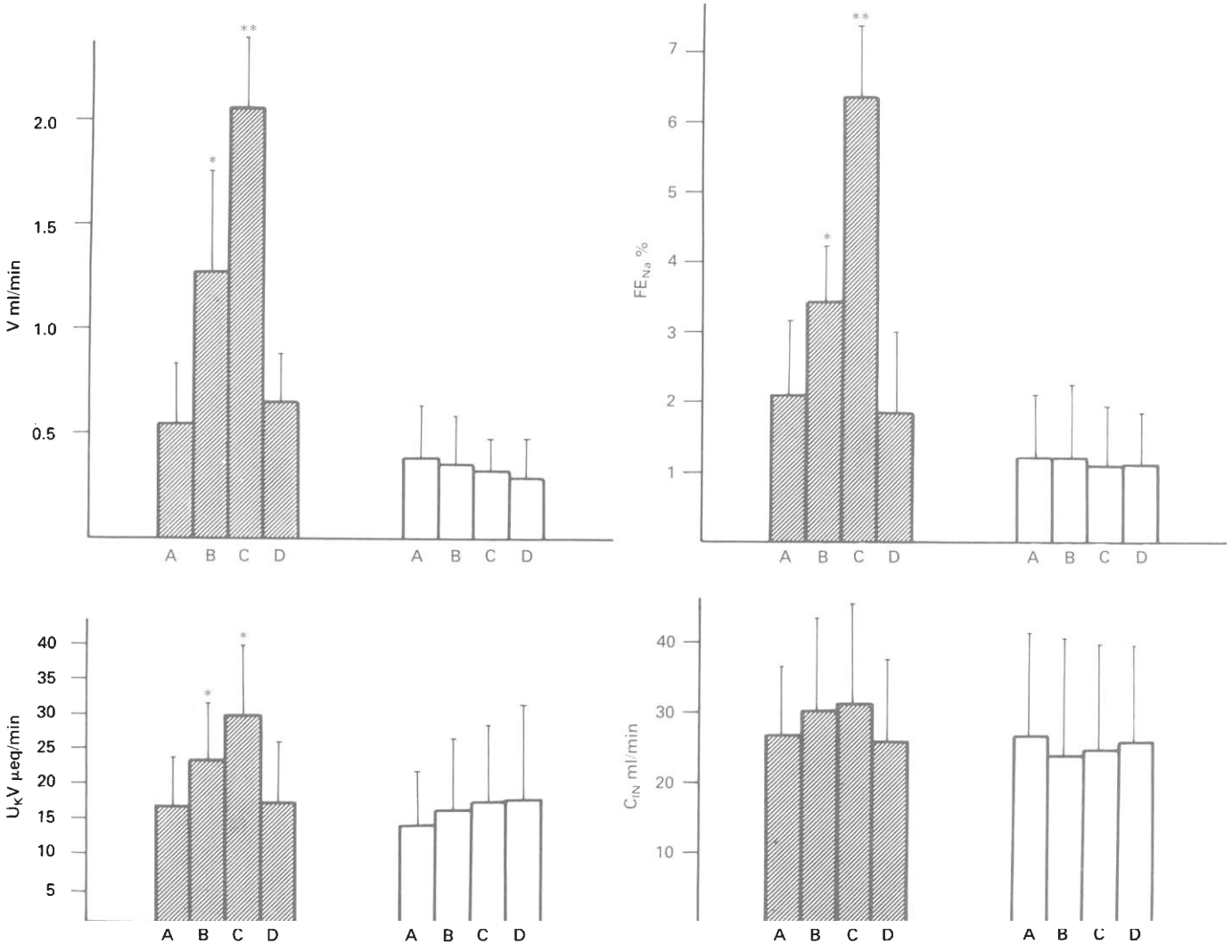

Fig. 3. *Effect of unilateral infusion of diluted bile on the flow of urine and on the rate of electrolyte excretion.* Note the ipsilateral increase in the flow of urine and electrolyte excretion during the intrarenal infusion of bile. Infusions were: A, 0.9% NaCl; B, bile diluted 1:20; C, bile diluted 1:10, D, 0.9% NaCl. Cross-hatched columns represent the ipsilateral (experimental) kidney, open columns the contralateral (control) kidney. $*P < 0.05$ (versus A); $**P < 0.01$ (versus A). Results are expressed as means ± SD. (Reprinted by permission from *Clin Sci*, © 1982, The Biochemical Society, London [11].)

As is well known, alcoholism is associated with alcoholic cardiomyopathy as well as with a characteristic decrease in the concentration of blood calcium, magnesium, inorganic phosphate, and potassium. All these changes, by themselves, could adversely affect cardiac function. Moreover, intracellular skeletal muscle content of calcium and sodium is increased and that of phosphate, magnesium, and potassium is decreased. These changes are conducive to the development of rhabdomyolysis of chronic alcoholism, as described by Knochel [29]. It is conceivable that parallel changes in intracellular electrolyte and mineral content occur also in the myocardium. To further clarify the effect of liver damage on cardiac function in the absence of interference by chronic alcoholism, we studied myocardial performance in two canine experimental models: dogs with choledochocaval anastomosis (CDCA), a model that produces isolated cholemia [30], and dogs with chronic bile duct ligation (CBDL) [31–33], a model that produces extensive liver fibrosis. The latter canine model (CBDL) closely resembles Laennec's cirrhosis in humans and is accepted as such by hepatologists (see Table 2). The CDCA dogs had extreme cholemia (bilirubin 40–60 mg/dl) but minimal parenchymal damage. We studied the effect of cholemia on multiple parameters of cardiac function in unanesthetized trained animals [34, 35]. These measurements included: (*1*) systolic time intervals; (*2*) pre-ejection period (PEP), which estimates the rate of ventricular pressure development [36, 37]; (*3*) left ventricular ejection time (LVET), which estimates stroke volume; and (*4*) dP/dt, a measure of the rate of increase in systolic pressure over time. We found that cholemia was associated with a twofold prolongation of PEP, a 15% shortening of LVET, an increase in the ratio of PEP/LVET, and a decrease in dP/dt. All these changes were statistically significant and suggested impairment in myocardial contractility [36, 38].

We extended these in-vivo studies by measuring in vitro the

Table 1. Factors causing underfilling of the circulation in chronic liver disease in humans and in experimental animals

1. Peripheral vasodilation and blunted vasoconstrictor responses to reflex, chemical, and hormonal influences.
2. Opening of arteriovenous and portal-systemic shunts.
3. Increase in the vascular capacity of the portal as well as the nonportal circulation.
4. Loss of fluid from the vascular compartment associated with hypoalbuminemia and decreased oncotic pressure.
5. Diminished venous return due to tense ascites.
6. Impaired left ventricular performance.
7. Occult gastrointestinal bleeding from ulcers, gastritis, or varices.
8. Volume losses due to vomiting, diarrhea, and excessive use of diuretics.

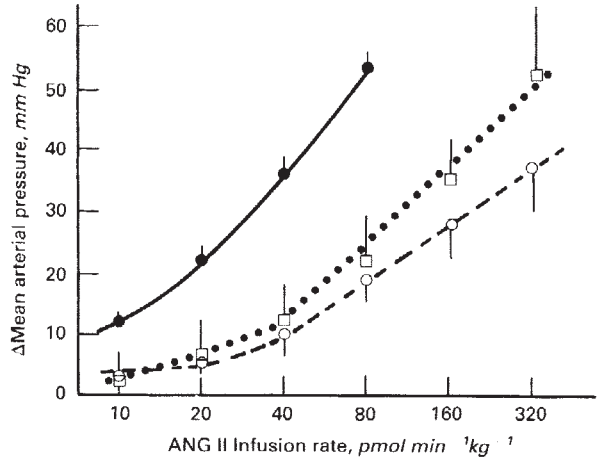

Fig. 4. *Increase in mean arterial pressure (mm Hg) in response to intravenous infusion of angiotensin II (ANG II) before (●---●), 1 week (○---○), and 3 weeks (□-----□) after ligation of the common bile duct in conscious dogs.* Results shown are means ± SEM. For control and 1 week data, n = 6; at 3 weeks, n = 5. Similar findings were obtained for noradrenaline infusion. Note blunting of pressor response to angiotensin II following bile duct ligation in these conscious dogs. (Reprinted by permission from *Clin Sci*, © 1981, The Biochemical Society, London [23].)

Table 2. Characteristic pathophysiologic features of the canine, chronic bile-duct ligation model that mimic those in patients with Laennec's cirrhosis

1. Liver histology showing bridging fibrosis and nodular formation [33][a].
2. Peripheral vasodilation and arterial hypotension [32, 33].
3. Increased cardiac output [32, 33].
4. Intrahepatic and portal hypertension with portal-systemic shunting [33].
5. Avid salt and water retention with formation of ascites and edema [31].
6. Impaired urinary dilution [31].
7. Blunted pressor responsiveness to the action of angiotensin II and norepinephrine [23].
8. Reversible renal failure following administration of nonsteroidal antiinflammatory agents [57].

[a] Numerals in brackets are reference numbers.

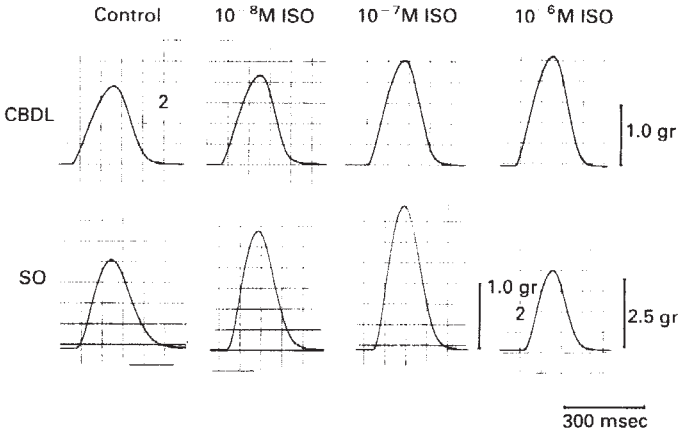

Fig. 5. *Representative records showing the effects of isoproterenol (iso) on the in-vitro isometric twitch from ventricular muscle from chronic bile duct-ligated dogs* (CBDL) *and from sham-operated dogs* (SO). Basic cycle length of electrical stimulation = 2000 ms. In the lower panel, note different calibration for the extreme right record. Active tension is reduced in the myocardial tissue from CBDL dog. (Reprinted by permission from *Clin Sci*, © 1985, The Biochemical Society, London [37].)

contractile response to the beta-adrenergic agonist isoproterenol in trabecular heart muscle taken from dogs with either CDCA or CBDL [37] (see Figs. 5, 6A, 6B). We found that the inotropic response to isoproterenol was blunted in the myocardial tissue obtained from both these models. Analysis of the data suggested that the blunted response to isoproterenol involved interferences with the binding of this agent to its membrane receptor. These findings are consistent with the preliminary reports by Lebrec and coworkers that there is resistance to the positive chronotropic action of isoproterenol in patients with cirrhosis and in rats with chronic bile duct ligation [39, 40].

Our studies have also shown that bile salts in concentrations of 10^{-8} to 10^{-6} molar depressed the contractile force of electrically stimulated myocardial tissue taken from normal rats (Binah O, Bomzon A, Better OS, unpublished data). Electrophysiologic studies in these experiments demonstrated that bile acids shortened the duration of the action potentials. This observation suggests that bile acids interfered either with the entry of calcium ions into, or with the exit of potassium from, the myocardial cells.

Taken together, these studies show that chronic liver damage, cholemia, or both exert a vasodepressor and cardiodepressor influence. Increase in circulating bile salts during cholestasis contributes to this phenomenon, but other, as yet unidentified, biliary compounds [13] as well as endotoxemia [41] and an increase in circulating leukotrienes [42, 43] also have a cardiodepressor influence.

The studies I have cited make it possible to formulate a comprehensive hypothesis regarding the clinical course of the patient under discussion. I propose that she was protected from salt retention for years by the natriuretic activity attributable to increased circulating bile salts. When, after 23 years of illness, hypoalbuminemia and portal hypertension appeared, this natriuretic tendency was overwhelmed by factors summarized in Table 1, and avid sodium and water retention led to the formation of ascites and edema. In her final admission she was hypotensive; this complication can be attributed not only to

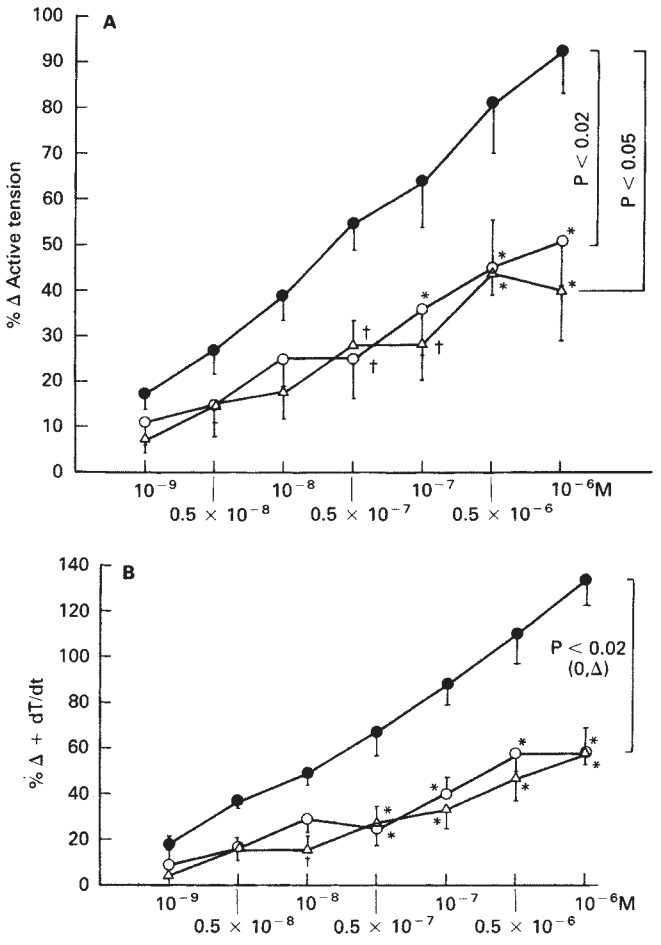

Fig. 6. *Effect of isoproterenol on isometric twitch indices from sham-operated and chronic bile duct-ligated dogs.* **A** Active tension. **B** Maximum rate of tension activation (+ dT/dt). Abscissa, molar concentrations of isoproterenol; ordinate, % change in a given variable compared with control; ●, sham-operated dogs (n = 9); ○, chronic bile duct-ligated dogs (n = 5); △, choledochocaval anastomosed dogs (n = 5). For each twitch parameter, dose-response curves from the control and any jaundiced groups were compared using two-way analysis of variance (ANOVA). The *P* value for the ANOVA test is shown on the right-hand side of the figure (6A and 6B). Student's *t*-test was used to compare individual doses: $*P < 0.01$; $\dagger P < 0.05$. Note: attenuation of indices of contraction in myocardial tissue taken from CBDL dogs. (Reprinted by permission from *Clin Sci*, © 1985, The Biochemical Society, London [37].)

redistribution of extracellular fluid, but also to vasodepressor and cardiodepressor influences of cholemia. The cardiovascular depressor effect aggravated the underfilling of the circulation and contributed to the development of the hepatorenal syndrome late in her course. It is noteworthy that despite the severe azotemia (serum creatinine 3.5 mg/dl), the kidney was able to concentrate the urine above the osmolality of the plasma and absorbed sodium avidly, a pattern that is consistent with functional renal failure.

I have discussed today the course of a patient with PBC. This interesting disease comprises only 2% of all instances of cirrhosis in humans. What implications from our animal studies can be extrapolated to the much more common affliction of alcoholic cirrhosis? Alcoholic cirrhosis is, of course, one of the leading causes of death during the years of gainful employment in the United States and Europe. As Table 2 illustrates, the dog with established CBDL is a useful experimental model for Laennec's cirrhosis in humans (even though, in the first postoperative week, the findings are more reminiscent of obstructive jaundice). Thus, the CBDL dog allows one to study longitudinally the pathophysiology of early cirrhosis. Our in-vivo and in-vitro studies cited today in the CBDL dog clearly show that the entire cardiovascular tree is depressed in this condition and thus presumably in Laennec's cirrhosis as well. Such effects would contribute further to the adverse influences of alcoholic cardiomyopathy, malnutrition, and cholemia on the circulation in patients with cirrhosis. The resulting cardiovascular depression contributes to the underfilling of the circulation and to arterial hypotension. In moderately advanced cirrhosis this functional disorder leads to the "prerenal" pattern, with avid sodium and water retention. In advanced cirrhosis, "underfilling" alongside the factors listed in Table 1 is the background on which the hepatorenal syndrome or even acute tubular necrosis occurs.

I would like to end this discussion by acknowledging that my interest in liver-kidney interrelationships was inspired by the extensive contribution to this field by the late Solomon Papper who died on 19 August 1984. His personal courage and affirmation of life even in the face of impending death are evident in the posthumously published article entitled "Care of patients with incurable chronic neoplasm. One patient's perspective" [44].

Questions and answers

DR. JEROME P. KASSIRER: You showed a series of events that occur in the course of progressive liver disease that can cause an acute decline in renal function. The patient with primary biliary cirrhosis whom you described today remained stable with normal renal function for many years. Typically, in the patient with alcoholic cirrhosis, deterioration in renal function is preceded by hypovolemia, secondary to the use of a diuretic or to paracentesis. In the final stage, your patient had no overt signs of heart disease, no reasons for nutritional or alcoholic cardiomyopathy, and the jaundice was stable. I don't understand why she suddenly developed the hepatorenal syndrome. Could you speculate on this question?

DR. BETTER: As is often the case, the hepatorenal syndrome may manifest itself in advanced liver disease without an apparent precipitating cause. At the end of her long illness, she was frankly cirrhotic. There was total distortion of the architecture of her liver, with deterioration of parenchymal liver function, and she had hypoalbuminemia and portal hypertension, which led to tense ascites. Thus, she behaved like many patients with end-stage cirrhosis.

Many of the factors enumerated in Table 1 operated in this patient to impair systemic hemodynamics and thereby to compromise renal function. It is difficult to pinpoint the exact cause of the hepatorenal syndrome, but if jaundice contributed to it, perhaps it was through an adverse effect on the circulation rather than via a direct effect on the kidney.

DR. KASSIRER: You clearly described the diuretic action of bile salts. Is it possible that the diuretic effect is related to the effect of the bile acid as a large anion? Is it the same as giving a load of nonreabsorbable anion, such as phosphate or sulfate, to a patient who is avidly retaining salt? Under such circum-

stances there is an increase either in hydrogen, potassium, or even in sodium in the urine. Could bile acids act as nonreabsorbable anions rather than as a diuretic?

DR. BETTER: The fact that intrarenal bile is still diuretic even at a dilution of 1:250 [13] renders this possibility unlikely. The concentration of nonreabsorbable anion at such dilution in the tubular fluid should be negligible. I therefore believe that bile salts act pharmacologically like a diuretic rather than like sulfate or phosphate, or osmotically like mannitol.

DR. O. ZINDER (*Chief, Laboratory for Clinical Biochemistry, Rambam Hospital*): There were reports that bile acids interfere with the action of sodium-potassium ATPase [45]. Is it possible that bile acids in your models interfere with sodium-potassium ATPase activity in the heart muscle or in the kidney? If so, it could explain cardiac and renal dysfunction as well as the increase in intracellular sodium that you quoted as being present in cirrhosis.

DR. BETTER: Your point is well taken. There are data suggesting that an increase in bile salts in the gut interferes with sodium-potassium ATPase activity and thus decreases sodium reabsorption and, secondarily, water reabsorption and thus causes diarrhea [45, 46]. Similarly, an increase in circulating bile acids could interfere with the activity of this enzyme in the brain and aggravate the metabolic disturbance of hepatic coma, partially by increasing the sodium content of brain cells [47]. We did not study the sodium-potassium ATPase activity of tissues during jaundice. We believe that the natriuretic action of bile acid is mediated by increased synthesis of renal PGE_2 rather than by blocking of the sodium-potassium ATPase. A circulating, ouabain-like sodium pump inhibitor (natriuretic hormone) was proposed by de Wardener [48], Haddy [49], and Blaustein [50] as the cause of some forms of hypertension. This hormone is thought to block sodium extrusion from cells leading to an increase in intracellular sodium and, secondarily, also calcium. Such a change in intracellular composition would increase vascular smooth muscle contractility and thus increase total peripheral resistance. In chronic liver disease, however, we have the exact opposite situation, namely, vasodilation, hypotension, and antinatriuresis. So if a circulating inhibitor to sodium-potassium ATPase is increased in cirrhosis, its physiologic action on the heart and kidney is masked.

PROF. H. E. ELIAHOU (*Chief, Department of Nephrology, Chaim Sheba Medical Center, Tel Aviv*): Many paradoxes were raised by your discussion and I wonder how you will reconcile them. (*1*) If your proposition is that bile salts can act on the heart in a similar fashion to calcium channel inhibitors, then they should be protective to the kidney. We and others have shown that such agents protect against experimental acute renal failure. Yet we all know that jaundiced and cirrhotic patients are susceptible to acute renal failure. (*2*) You spoke loosely about acute renal failure occurring in end-stage cirrhosis and in cholemia. Yet you described the prerenal nature of renal failure and not acute tubular necrosis, in which the urine is isoosmotic and sodium excretion increased. Could you clarify these paradoxes?

DR. BETTER: Yes, indeed, we have a paradox. Several effects of high circulating bile acids should protect the kidney from acute tubular necrosis in patients with advanced cirrhosis and cholemia. They include (*1*) nifedipine-like effect, and (*2*) stimulation of renal PGE_2 synthesis and decreased coagulability of the blood. Yet such patients are prone to ATN. I believe the reason is that the maldistribution of blood and interstitial fluid as well as the vaso- and cardiodepressor effect of cholemia cause an "underfilling" of the circulation and hypotension (see also Table 1), which in turn cause prerenal failure. When this situation is protracted, any protective influences on the kidneys are overridden, and prerenal failure will be transformed into ATN. The vasoconstrictor influences of endotoxin [41] and renal thromboxane A [51] may mediate such a transition. It is, however, the metabolic and hemodynamic environment rather than parenchymal renal disease that leads to this renal failure. When the metabolic and hemodynamic environment is normalized by successful liver transplantation [52], or by transplantation of hepatorenal kidneys into recipients with normal livers [53], renal function improves. In other words, the hepatorenal syndrome is reversed.

DR. KASSIRER: Would you argue that the heart is at fault in the hepatorenal syndrome?

DR. BETTER: Not only the heart but the entire cardiovascular system is depressed in the hepatorenal syndrome. In this disorder arterial hypotension is due predominantly to decreased peripheral resistance. Myocardial dysfunction is present but plays a lesser role in decreasing blood pressure.

DR. A. HARAMATI (*Visiting Scientist, Department of Physiology and Biophysics, Mayo Clinic and Mayo Foundation, Rochester, Minnesota, USA*): You made the statement that in experiments performed by Dr. Uri Alon of your laboratory, indomethacin blocked the diuretic effect of bile salts. Indeed, a rise in PGE_2 would explain both the increase in renal blood flow and the natriuresis. Are you reasonably convinced that the diuretic effect of bile salts is mediated by PGE_2? You were not clear about such a connection. We are left with the impression that bile salts are directly diuretic and that the increase in urinary PGE_2 is a secondary phenomenon.

DR. BETTER: We believe that bile acids are natriuretic by virtue of their stimulation of renal PGE_2 synthesis. Similar doubts exist concerning the effects of indomethacin on the diuretic action of furosemide in normal humans and animals. Depending on the sodium balance of the individual and the dosage of indomethacin, you can block the natriuretic effect of furosemide with this drug. The results of these experiments in the literature are not clear-cut [54]. But the situation in patients with cirrhosis is unequivocal. In cirrhosis, nonsteroidal antiinflammatory agents abolish the natriuretic action of furosemide [55].

DR. HARAMATI: Could some of the derangements in volume control and renal handling of sodium that you described today be due to a disturbance in the excretion of copper in a patient with primary biliary cirrhosis?

DR. BETTER: The hepatobiliary system is the main excretory route for body copper. In biliary cirrhosis, destruction of the intrahepatic biliary ducts results, among other things, in retention of copper and in an increase of blood and tissue copper, similar to that in Wilson's disease. The pathologist found an increase in copper content of the liver in the patient described today. One would expect an increase in copper also in bone, heart, and kidney. This might explain the severe osteopenia that occurs in biliary cirrhosis and that complicates the vitamin D-dependent osteomalacia in this disease. Copper deposits in the tubules—analogous to what occurs in Wilson's disease—can

cause proximal and distal tubular acidosis and perhaps also the exaggerated natriuresis that we have described in primary biliary cirrhosis.

DR. J. BERNHEIM (*Chief, Department of Nephrology, Bet Meir Hospital, Kfar Saba, Israel*): I'd like to return to the role of PGE_2 in the natriuresis induced by bile salts. The increase in natriuresis and in PGE_2 excretion that you found following intrarenal injection of bile was abolished by indomethacin; this observation is not necessarily proof that the diuretic effect of bile is PGE_2 mediated. There are many discrepancies between urinary PGE_2 excretion and natriuresis. In cirrhosis, urinary PGE_2 is high, yet the kidney retains sodium. Changes in PGE_2 excretion can be nonspecific and are influenced by the urine volume. In your experiments, changes in urinary PGE_2 excretion could merely reflect fluctuation in urine volume. I do not believe that a decrease in both urinary PGE_2 and sodium excretion following indomethacin in your experiments necessarily proves a causal connection between renal PGE_2 synthesis and natriuresis.

DR. BETTER: This issue is not yet settled. I do know that Wernze and Goerig in West Germany regularly find that the levels of urinary PGE_2 are greater in primary biliary cirrhosis than in Laennec's cirrhosis (personal communication, 1985).

DR. A. BOMZON (*Department of Pharmacology, Faculty of Medicine, Technion-Israel Institute of Technology, Haifa*): From what we heard today, bile salts appear to be magic substances having a variety of interesting influences. They block sodium-potassium ATPase, inhibit calcium influx, and interfere with adrenergic receptors. In the experiments of Binah et al that you described [37], the effects of bile salts were seen at concentrations of 10^{-7} M. What were the concentrations of bile salts in the experiments that showed a natriuretic effect of bile?

DR. BETTER: Acute bile duct ligation or choledochocaval anastomosis in our hands regularly causes an immediate, striking diuresis in the dog. Levy calculated the increase in bile salts in the blood following acute bile duct ligation in the dog and found it to be in the micromolar range [12, 13]. Thus, although Alon et al may have injected a pharmacologic dose of bile salts intrarenally, these compounds also are natriuretic in the physiologic range.

DR. KASSIRER: You assume that the entire effect on the kidney is due to bile salts. How can you be sure that other substances are not having an effect?

DR. BETTER: I believe that the natriuretic effect is due to bile salts, because removing them from bile by dialysis or absorption with cholestyramine abolishes the natriuretic activity of bile [13]. Bile acid, however, is not the factor in bile that is capable of increasing glomerular filtration rate and renal plasma flow after acute bile duct ligation. The nature of the bile compound that has vasodilatory properties remains unknown.

DR. U. ALON (*Department of Pediatric Nephrology, Rambam Hospital*): Although jaundice interferes with cardiac performance, the main reason for the hypotension is peripheral vasodilation. Do you have an explanation for this disorder and for the blunted response to pressor agents in chronic liver disease?

DR. BETTER: Your point is well taken. Peripheral vasodilation is the main cause of the hypotension in liver disease; the heart plays only a secondary role. The reason for the vasodilation is not clear. One possible explanation is that vasodilatory hormones from the intestines (such as glucagon, VIP, and substance P) bypass the liver or are inadequately degraded by the diseased liver and escape into the circulation. Thus, the systemic circulation is exposed to enhanced vasodilator activity. Another possibility is an increase in prostacyclin synthesis within the arteriolar wall. Such a possibility is supported by the finding of an increase in vascular responsiveness to angiotensin II in patients with cirrhosis who received indomethacin [56] and by the finding of an increase in arterial blood pressure in anesthetized, bile duct-ligated dogs following indomethacin administration [57]. Dr. Bomzon, are there any known explanations for the peripheral vasodilation of cirrhosis?

DR. BOMZON: Patients with cirrhosis have increased sympathetic tone as well as an increase in circulating catecholamines, yet they are hypotensive. This finding emphasizes the end-organ refractoriness to constrictor influences, be it the vascular smooth muscle or even the myocardium. The mechanism for this effect has not been defined.

DR. BETTER: I would like to add that humans and animals with liver disease are hypotensive in the presence of an increase in circulating angiotensin II, arginine vasopressin, and catecholamines, all powerful vasoconstrictors under normal conditions. Finding elevated levels in the presence of moderate hypotension does not mean that these hormones do not participate in the defense of blood pressure; blocking their activity can precipitate much more profound hypotension in patients with liver disease.

DR. P. SZYLMAN (*Chief, Division of Nephrology, Poriah Hospital, Tiberias, Israel*): You utilized phosphate clearance as a marker for proximal tubular function in your experiments in patients with biliary cirrhosis. Is the use of phosphate clearance for this purpose justified in this disease, given the aberration in vitamin D metabolism that occurs?

DR. BETTER: Vitamin D metabolism is grossly disturbed in biliary cirrhosis [58]. A lack of bile acids in the gut interferes with the absorption of fat and the fat-soluble vitamins A, D, E, and K. Steatorrhea, by itself, also diminishes calcium absorption. The diminished quantity of vitamin D that is absorbed may not be adequately hydroxylated by the diseased liver and can result in subnormal levels of 25(OH)D and its active metabolites. It is no wonder that patients with biliary cirrhosis are hypocalcemic and can suffer from florid osteomalacia. I agree with you that under the influence of secondary hyperparathyroidism and hyperphosphaturia characteristic in this condition, the renal clearance of phosphate is not a good marker for proximal tubular function.

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