Hepatorenal Syndrome: Emerging Perspectives of Pathophysiology and Therapy

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ABSTRACT
Progressive oliguric renal failure (designated "hepatorenal syndrome") commonly complicates the course of patients with advanced hepatic disease. Despite the severe derangement of renal function and ominous prognosis when renal failure develops, minimal and inconsistent pathologic abnormalities of the kidneys are found at autopsy. Furthermore, the kidneys, if transplanted, are capable of normal function, which supports the concept that the renal failure is functional and potentially reversible. In contrast to patients with classical acute failure (ATN), hepatorenal syndrome patients manifest characteristic alterations of renal function including (1) relatively hyperosmolar urine; (2) high creatinine urine:plasma ratio, and (3) a very low urine sodium concentration (<10 mEq/L). The past several years have witnessed newer insights into both the pathophysiology and the therapeutics of this syndrome. The application of newer methodology such as tracer kinetics has more rigorously delineated the role of a number of pathogenic mechanisms including activation of the sympathetic nervous system. The characterization of endothelin and the nitric oxide (NO)-arginine pathway and their roles in biology and medicine has provided additional new insights with regard to the pathogenesis of hepatorenal syndrome. For example, nitric oxide has been proposed to constitute a mediator of both the hyperdynamic circulation and renal failure. Finally, recently initiated therapeutic approaches lend a note of optimism to the future management of a syndrome that is so often incompatible with recovery. These include the acceptance of orthotopic liver transplantation as definitive treatment for patients with end-stage liver disease and attempts to improve renal function by countervailing the decreases in systemic vascular resistance while minimizing concomitant increments in renal vascular resistance. Hopefully, ongoing and future clinical trials will establish the precise contribution of each of these treatment modalities and their respective roles in the therapeutic armamentarium.

Key Words: Oliguric renal failure, cirrhosis, endothelin, nitric oxide, hepatic transplantation

The hepatorenal syndrome (HRS) is a unique form of acute renal failure occurring in patients with liver disease for which a specific cause cannot be elucidated. Despite the intense clinical and investigational interest that this syndrome has stimulated, until recently, relatively little progress had been made in the understanding and management of this syndrome. The past several years have witnessed newer insights in both the pathophysiology and therapeutics of this syndrome. The application of newer methodology such as tracer kinetics has more rigorously delineated the role of a number of pathogenic mechanisms, including activation of the sympathetic nervous system. The characterization of endothelin and the nitric oxide (NO)-arginine pathway and their roles in biology and medicine has provided additional new insights with regard to the pathogenesis of HRS. Finally, recently initiated therapeutic approaches lend a note of optimism to the future management of a syndrome that is so often incompatible with recovery.

It is not my intent to compile an exhaustive survey of the pathophysiology and therapeutics of the HRS. Rather, emphasis will be on selective issues that I believe are timely and have recently attracted increased attention and investigative interest.

CLINICAL FEATURES
Progressive oliguric renal failure commonly complicates the course of advanced hepatic disease (1-
Although this condition has been designated by many names—including "functional renal failure," "hemodynamic renal failure," "hepatic nephropathy," the "renal failure of cirrhosis," and others—the more appealing, albeit less specific, term "HRS" is the most commonly used. For the purpose of this discussion, HRS 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.

The clinical features of HRS have been detailed in several recent reviews (1-4). In brief, HRS usually occurs in cirrhotic patients who are alcoholic, although cirrhosis is not a sine qua non for the development of HRS. HRS may complicate other liver diseases, including acute hepatitis, fulminant hepatic failure, and hepatic malignancy (5-7). Although renal failure may develop in patients in whom normal serum creatinine levels have been previously documented within a few days of the onset of HRS, this does not imply that these patients had a normal GFR. The serum creatinine level has been shown to be a poor index of renal function in patients with chronic liver disease, often masking markedly reduced GFR (7). Implicit in such a formulation is the concept that HRS patients may have a low GFR for weeks to months before coming to medical attention. We are therefore dealing with kidneys that are almost certainly susceptible to further insult by hemodynamic or other stimuli.

Numerous reports have emphasized the development of renal failure after events that reduce effective blood volume, including abdominal paracentesis, vigorous diuretic therapy, and gastrointestinal bleeding, although renal failure can occur in the absence of an apparent precipitating event. In this context, several careful observers have noted that HRS patients seldom arrive in the hospital with preexisting renal failure; rather, HRS seems to develop in the hospital, indicating that iatrogenic events in the hospital might precipitate this syndrome (1,4).

The development of renal failure in the course of Laënnec's cirrhosis is of grave prognostic significance (1,4,8). The majority of patients die within 3 wk of the onset of azotemia. Despite the bleak prognosis, it is difficult to attribute the poor outcome directly to renal failure in patients in whom azotemia is moderate. Such observations suggest that the renal failure may be more of a reflection of a broader lethal event and that, in most instances, it is not in itself the major determinant of survival. A truly uremic death is a rarity.

PATHOGENESIS

A substantial body of evidence lends strong support to the concept that the renal failure in HRS is functional in nature. Despite the severe derangement of renal function, pathologic abnormalities are minimal and inconsistent (1,4,9). Furthermore, tubular functional integrity is maintained during the renal failure, as manifested by a relatively unimpaired sodium reabsorptive capacity and concentrating ability. Finally, more direct evidence is derived (1) from the demonstration that kidneys transplanted from patients with HRS are capable of resuming normal function in the recipient (10) and (2) by the return of renal function when the patient with HRS successfully receives a liver transplant (11).

Despite extensive study, the precise pathogenesis of HRS has not been delineated. Many studies using diverse hemodynamic techniques have documented a significant reduction in renal perfusion (12-14). Because a similar decrement of renal perfusion is compatible with urine volumes exceeding 1 L in many patients with chronic renal failure, it is unlikely that a decrease in mean blood flow per se is responsible for the encountered oliguria (15).

Our laboratory applied the 133Xe washout technique and selective renal arteriography to the study of HRS and demonstrated a significant reduction in calculated mean blood flow as well as a preferential reduction in cortical perfusion (13). In addition, cirrhotic patients manifested marked vasomotor instability that was characterized not only by variability between serial xenon washout studies but also by instability within a single curve (13). This phenomenon has not been encountered in renal failure of other causes. In addition, Epstein and coworkers (13) performed simultaneous renal arteriography to delineate further the nature of the hemodynamic abnormalities. Selective renal arteriograms disclosed marked beading and tortuosity of the interlobar and proximal arcuate arteries and an absence of distinct cortical nephrograms and vascular filling of the cortical vessels (Figure 1A). Postmortem angiography performed on the kidneys of five patients studied during life disclosed a striking normalization of the vascular abnormalities with a reversal of all of the vascular abnormalities in the kidneys (Figure 1B). The peripheral vasculature filled completely, and the previously irregular vessels became smooth and regular. These findings provide additional evidence for the functional basis of the renal failure, operating through active renal vasoconstriction (13).

Although renal hypoperfusion with preferential renal cortical ischemia has been shown to underlie the renal failure of HRS (13,16), the factors responsible for sustaining reduction in cortical perfusion and suppression of filtration in HRS have not been elucidated. A consideration of the pathogenetic events leading to the intrarenal hemodynamic derangement and the decrease in GFR is simplified by a consideration of the "afferent" and "efferent" events.
that lead to this derangement. The discussion of afferent events will include a consideration of the extracellular fluid translocations or sequestration into serous spaces or interstitial fluid compartments that characterize advanced liver disease. The section considering efferent events will encompass a survey of the hormonal and neural mechanisms proposed or implicated in the pathogenesis of the renal failure. Emphasis will be placed on recent studies characterizing the sympathetic nervous system, renal thromboxanes (Tx), (NO)-arginine pathway, and the possible contribution of endothelin.

**Afferent Events**

Traditionally, it has been proposed that a contraction of the "effective" blood volume constitutes a pivotal event in patients being predisposed to HRS (1-4,17-19). In this context, it is important to note that the term "effective plasma volume" refers to that part of the total circulating volume that is effective in stimulating volume receptors. The concept is somewhat elusive because the actual volume receptors remain incompletely defined. A diminished effective volume may reflect subtle alterations in systemic hemodynamic factors such as decreased filling of the arterial tree, a diminished central blood volume, or both. Despite massive retention of salt and water, effective blood volume remains functionally contracted because of a disturbance in the Starling forces, which govern the distribution of fluid within the extracellular fluid compartment.

The mechanisms contributing to the appearance of a diminished effective volume are multiple. Traditionally, it has been proposed that ascites formation in cirrhotic patients begins when a critical imbalance of Starling forces in the hepatic sinusoids and splanchnic capillaries causes an excessive amount of lymph formation, exceeding the capacity of the thoracic duct to return this excessive lymph to the circulation (1,17-19). Consequently, excess lymph accumulates in the peritoneal space as ascites, with
a subsequent contraction of circulating plasma volume. Thus, as ascites develops, there is a progressive redistribution of plasma volume.

Although an imbalance of Starling forces in the hepatopancreatic microcirculation is thought to contribute importantly to the relative decrease in effective blood volume, it should be emphasized that this is not the sole mechanism. An additional determinant is the significant diminution of total peripheral resistance in most patients with cirrhosis who are retaining sodium and water (20,21). This decrease in peripheral vascular resistance is no doubt partially related to anatomical arteriovenous shunts, and possibly to some undefined vasodilator (either produced by or not inactivated by the diseased liver). Thus, despite an increase in total plasma volume, the relative "fullness" of the arteriovenous tree is diminished.

In summary, several hemodynamic events act in concert to diminish effective volume, thereby activating the mechanisms promoting a decrease in renal perfusion and GFR. Regardless of cause, the resultant diminution of effective volume is thought to constitute an afferent signal to the renal tubule to augment salt and water reabsorption and to decrease GFR. Thus, the traditional underfill formulation suggests that the renal retention of sodium is a secondary rather than a primary event.

Peripheral Arterial Vasodilation Theory (Revised Underfill Theory). The principal distinguishing feature of a newly proposed revision of the underfill theory is that the decrease in effective blood volume is attributable primarily to an early occurring increase in vascular capacitance (21). Thus, peripheral vasodilation is the initial determinant of intravascular underfilling, and an imbalance between the expanded capacitance and available volume constitutes a diminished effective volume. This concept brings the hypothesis into accord with some experimental observations that were not consistent with the original postulate. For example, recent careful balance studies in animals with experimental cirrhosis have clearly shown that sodium retention precedes ascites formation (22).

Primary systemic hemodynamic changes characterized by peripheral vasodilation occur very early in experimental cirrhosis and in humans with compensated cirrhosis (20,22,23). The decrease in effective volume induced by these hemodynamic alterations is compounded further by an impaired pressor response to vasoactive agents, including exogenous angiotensin II and noradrenaline (4,21). Even in those patients who eventually develop an increase in total plasma volume, the relative "fullness" of the arteriovenous tree is decreased.

According to the peripheral arterial vasodilation hypothesis, the HRS constitutes an extreme extension of underfilling of the arterial circulation, with the most extreme elevations of vasoactive hormones, including PRA, norepinephrine (NE), and vasoprespin, and the most extreme degree of renal vasoconstriction (21).

Overflow Theory. An alternative hypothesis to the two underfill theories is the overflow theory of ascites formation (22,24). In contrast to the underfill formulation, the overflow theory postulates that the initial primary event is the inappropriate retention of excessive amounts of sodium by the kidneys, unrelated to defense of the plasma volume (and thought to be due to intrahepatic hypertension). In the setting of abnormal Starling forces in the portal venous bed and hepatic sinusoids (both portal venous hypertension and a reduction in plasma colloid osmotic pressure), the expanded plasma volume is sequestered preferentially in the peritoneal space, with resultant ascites formation. Thus, renal sodium retention and plasma volume expansion precede rather than follow the formation of ascites.

In summary, both underfill theories provide a possible explanation of why fluid retention often fails to attenuate both the stimulus for neurohormonal activation and the continuing sodium and water retention. Despite a progressive increase in total extracellular fluid volume, fluid is sequestered into one or more of the other fluid compartments without succeeding in normalizing effective blood volume. Because the capacity of the interstitial fluid and its associated spaces, for example, the peritoneum, is largely limitless, the kidneys encounter great difficulty in filling such a space and the sodium retention becomes relentless. Only correction of the disturbance in the forces governing fluid distribution and reversing the peripheral arterial vasodilation will permit a reexpansion of effective blood volume to normal. Importantly, the peripheral arterial vasodilation theory highlights the florid systemic hemodynamic disturbances and the importance of attempting to correct not only the renal hemodynamic disturbances but the concomitant systemic hemodynamic derangements as well.

An alternate formulation has emphasized that the renal vasoconstriction is attributable to unique events independent of a contracted volume, i.e., a primary cause. According to this theory, advanced liver damage, in conjunction with some other unknown abnormality, induces a primary disorder in one or more of the modifiers that regulate renal vascular tone. The renal ischemia, it is argued, is not an expression of the normal neural and hormonal response to liver damage but rather represents either an alteration in the synthesis, degradation, or potency of a vasoactive substance or a malfunction of the normal feedback regulation of its release. Such abnormalities might result from impaired hepatic degradative or excretory capacity, portasystemic...
shunting of blood, or altered neural connections between the liver and the kidney.

Although many investigators have focused on a contraction of effective arterial blood volume (EABV) as a major etiologic factor in the pathogenesis of HRS, there is lack of unanimity on this point. Some authors have proposed that because a diminished EABV causes the typical syndrome of prerenal failure (easily reversible with volume replacement) sometimes leading to ATN, it cannot be considered as the prepotent etiologic factor for HRS. Although I agree that because HRS is primarily a syndrome induced by a unique cause for renal ischemia not necessitating a contracted EABV, a contributory role for a contracted EABV need not be excluded. Rather, it is tempting to postulate that a contracted EABV or the concomitant activation of neurohormonal mediators that attend such hypovolemia amplifies the renal vasoconstrictive effects of the putative, as yet undefined, mediators. Indeed, because the majority of studies have reported that a reduction of EABV is a typical feature of patients with HRS, this alteration in volume status may be a necessary but not sufficient factor predisposing patients to HRS.

An alternate formulation to reconcile the presence of contracted EABV in both prerenal azotemia and HRS posits that they represent differences in degree and occupy disparate points on a continuum (21). Conceivably, patients with moderate contraction of EABV develop prerenal azotemia, which is reversible by volume repletion. With advancing liver disease, the magnitude of the contraction becomes greater and at some point is no longer reversible by volume-expansive maneuvers. Presumably at this point, we are facing the transition from prerenal azotemia to HRS.

**Efferent Events**

The effectors that promote renal ischemia and a decrease in GFR remain incompletely defined. Several major hypotheses have been implicated or suggested, including: (1) alterations of the renin-angiotensin system; (2) an increase in sympathetic nervous system activity; (3) alterations in renal eicosanoids, including a relative decrease in renal vasodilatory prostaglandins and an increase in vasoconstrictor Tx; (4) enhanced NO production with peripheral vasodilation; (5) elevated plasma endothelin levels; (6) a relative impairment of renal kallikrein production; and (7) endotoxemia (Table 1).

**Renin-Angiotensin System.** Several lines of evidence suggest a role for the renin-angiotensin axis in sustaining the vasoconstriction in HRS (25). Patients with decompensated cirrhosis frequently manifest marked elevations of plasma renin levels (25–29). An examination of the relationship between renal func-

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**Neural and Hemodynamic**

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...tion and plasma renin levels has disclosed that cirrhotic patients with impaired renal function manifested the most profound elevations in plasma renin levels. Although the elevation of plasma renin is attributable in part to the decreased hepatic inactivation of renin, it is evident that the major determinant is increased renin secretion by the kidney. It is noteworthy that the elevation of plasma renin often occurs despite diminished hepatic synthesis of the α2 globulin, renin substrate (25).

There are at least two reasonable explanations for the increased renin secretion in cirrhosis. First, it is possible that renal hypoperfusion may be the primary event, with a resultant activation of the renin-angiotensin system. Alternatively, activation of the renin-angiotensin system may be a secondary response to a diminished effective blood volume.

The observations of Barnardo et al. (29) have been interpreted as supporting the former hypothesis. Those authors infused dopamine into 10 patients whose cirrhosis was associated with various degrees of renal functional impairment. Dopamine caused a consistent increase in effective RPF but little change in GFR or sodium and water excretion. Concomitantly, dopamine suppressed PRA. One might object that increases in arterial pressure or cardiac output occurring during dopamine administration could confound the interpretation of the results. Such a possibility did not pertain to this study, however, because dopamine was administered in subpressor doses and the changes in cardiac output were slight and inconsistent. Furthermore, it has been shown previously that dopamine given intravenously to normal subjects or directly into the renal artery of normal dogs does not reduce PRA (29). It is therefore unlikely that dopamine reduced renin secretion by directly affecting the juxtaglomerular apparatus. Rather, the ability of dopamine to reduce PRA is most probably attributable to its ability to increase pri-
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primarily RPF. In summary, the authors interpreted their findings as indicating that the increased PRA of cirrhosis is secondary to the impaired renal perfusion, rather than being its cause (29).

Regardless of mechanism(s), the activation of the renin-angiotensin system has profound implications for renal function. In light of compelling experimental evidence that angiotensin plays an important role in the control of the renal circulation (30), it is tempting to speculate that enhanced angiotensin levels contribute to the renal vasoconstriction and the reduction in filtration rate seen in the renal failure in cirrhosis. Observations by Cade et al. (31) have underscored the role of angiotensin II in mediating the reduction in renal perfusion and GFR in patients with HRS. The infusion of angiotensin II caused a marked reduction of RPF and GFR, with a marked increase in filtration fraction.

In addition to activation of the renin-angiotensin system, attention has focused on the possibility that the depletion of renin substrate may be the principal etiologic factor for the hemodynamic abnormalities that accompany HRS (32,33). Iwatsuki et al. (11) demonstrated that renin substrate levels rose significantly after hepatic transplantation and preceded the improvement in renal function by several days. Subsequently, Berkowitz et al. (33) infused renin substrate–rich fresh frozen plasma into two patients with HRS and noted a prompt increase in creatinine clearance and urine output coincident with a significant rise in renin substrate and in the suppression of peripheral renin concentration (34). After the termination of the infusion, both urine flow and creatinine clearance decreased progressively over the next 5 days as renin substrate concentrations declined toward preinfusion levels.

Cade et al. (31) have extended these observations. Those investigators administered either 750 mL of stored plasma or 750 mL of fresh frozen plasma in random order on successive days. The infusion of fresh frozen plasma improved function more than did stored plasma and in addition returned a very low filtration fraction toward normal. Plasma renin substrate concentration was uniformly low and was increased by an infusion of fresh frozen plasma. Arterial blood pressure, initially low, was improved by the infusion of stored plasma but increased far more when fresh frozen plasma was infused. The low filtration fraction observed in all of their patients was depressed even more by expansion with stored plasma but returned toward normal when fresh frozen plasma was infused (31). Only additional studies will establish the significance of these provocative observations.

The availability of pharmacologic agents that interrupt the renin-angiotensin axis has suggested a possible approach for defining further the role of angiotensin as a determinant of the state of the renal vasculature (see reference 37). Unfortunately, attempts to block the renin-angiotensin system in cirrhotic humans have been complicated by a striking fall in blood pressure and by the intrinsic activity of the partial agonists in use, which may have blunted the influence on GFR (35,36). The synthesis of more specific angiotensin antagonists that may act preferentially at the level of the renal vascular bed without inducing concomitant hypotension may contribute to the further characterization of the pathogenesis of HRS (37).

Role of Renal Prostaglandins. Alterations of renal prostaglandins also participate in mediating the renal failure of cirrhosis. Attempts to investigate the role of renal prostaglandins in modulating renal hemodynamics and mediating the sodium retention in cirrhosis have encompassed two manipulations: (1) the administration of exogenous prostaglandins and (2) the alteration of the endogenous production of prostaglandins by the inhibition of prostaglandin synthesis. Initially, the problem was approached by examining the renal hemodynamic response to the administration of exogenous prostaglandins (38). Unfortunately, the relevance of such studies in cirrhotic humans is tenuous because any action of prostaglandins on the kidney must be as a local tissue hormone (39). Thus, any evaluation of the physiologic role of prostaglandins in renal function necessitates an experimental design in which the endogenous production of the lipids is altered.

Several investigators have demonstrated that the administration of inhibitors of prostaglandin synthetase (both indomethacin and ibuprofen) resulted in significant decrements in GFR and effective RPF in patients with alcoholic liver disease and ascites (40,41). Of interest, the decrement in renal hemodynamics varied directly with the degree of sodium retention, i.e., the patients with the most avid sodium retention manifested the largest decrements in GFR (41–43).

Because the above-cited studies have examined the effect of inhibiting the endogenous production of renal prostaglandins, it was of great interest to assess an opposite experimental manipulation, i.e., assessing the effects of the augmentation of endogenous prostaglandins on renal function. Epstein and associates (44) have used water immersion to the neck, an experimental maneuver that redistributes blood volume with concomitant central hypervolemia and enhances prostaglandin E (PGE) excretion in normal humans. They demonstrated that decompensated cirrhotic patients manifested an increase in mean PGE excretion that was threefold greater than that observed in normal subjects studied under identical conditions (45). This was attended by a marked natriuresis and an increase in creatinine clearance.
When interpreted in concert with the earlier studies using prostaglandin synthetase inhibitors, these findings suggest that derangements in renal PGE production contribute to the renal dysfunction of cirrhosis. Specifically, it is tempting to postulate that, in the setting of cirrhosis of the liver, the ability to enhance prostaglandin synthesis constitutes a compensatory or adaptive response to incipient renal ischemia. The corollary of this formulation is that the administration of agents that impair such an adaptation can induce a clinically important deterioration of renal function.

The above findings are not isolated observations. As I have noted (43), one may conceive of renal prostaglandins as constituting critical modulators of renal function during conditions or disease states involving volume contraction. The demonstration that synthetase inhibition affected renal function only in decompensated (presence of ascites and/or edema) and not in compensated cirrhotic subjects and that the effects of synthetase inhibition vary as a function of the degree of renal sodium avidity is consistent with this formulation (42,43).

Additional studies have suggested that alterations of thromboxanes may contribute to the renal dysfunction. Thromboxane A₂ (TxA₂), a potent proaggregatory and vasoconstrictor substance, is synthesized by platelets and a large number of other cell types and tissues, including the kidney (46,47). Renal TxA₂ production is thought to be involved in the regulation of glomerular hemodynamics by acting on glomerular capillary filtration surface area (46,47) and by modulating the tone of afferent and efferent arterioles (47). It has been proposed that the ratio of the vasodilator PGE₂ to the vasoconstrictor prostaglandin TxA₂, i.e., E₂/TxA₂, rather than absolute levels of PGE₂, may determine the degree of renal vasoconstriction of HRS. Zipser et al. (48) determined the urinary excretion of PGE₂ and TxA₂ (the nonenzymatic metabolite of TxA₂) in 14 patients with HRS. They observed that, whereas PGE₂ levels were decreased in comparison with those of healthy controls as well as those of patients with acute renal failure, TxB₂ levels were markedly elevated. The authors interpreted their data to suggest that an imbalance of vasodilator and vasoconstrictor metabolites of arachidonic acid contribute to the pathogenesis of HRS.

It should be noted, however, that the findings of others of an increase in TxB₂ are somewhat different. Rimola et al. (49) studied 18 normal subjects, 49 cirrhotic patients with ascites (but without renal failure), and 20 patients with HRS. Cirrhotic patients without HRS had a significantly higher urinary excretion of 6-keto-PGF₁α, TxB₂, and PGE than did normal subjects. Patients with HRS failed to manifest increases in urinary PGE₂, 6-keto-PGF₁α, and TxB₂; this is in contrast to the findings of Zipser et al. (48). Rimola et al. (49) speculated that the discrepancy between their own findings and those of Zipser et al. (48) might have been attributable to differences in the patient population. Rimola et al. (49) studied patients with moderate impairment of hepatic and renal function, whereas the patients in the studies of Zipser et al. (48) had hepatic failure and severe renal insufficiency. Additional studies will be required to assess alterations in the differing eicosanoids with progressive renal functional impairment.

In light of the above findings suggesting that thromboxanes may contribute to the development of HRS, there have been attempts to modify the course of HRS by the administration of selective inhibitors of thromboxane synthesis and thromboxane receptor antagonists (50–52). As detailed on page 13, such interventions either have been negative or have failed to substantively augment GFR. Additional studies with thromboxane receptor antagonists in patients with widely varying degrees of acute renal insufficiency will be required to further define the role of TxA₂ as a major determinant of the renal vasoconstriction in HRS.

**Increase in Sympathetic Nervous System Activity.** An increase in sympathetic nervous system activity also contributes to the renal failure of cirrhosis. It is now well established that alterations of the input of cardiopulmonary receptors induce changes in renal sympathetic activity (53–56). Thus, a decrease in effective blood volume is sensed as a decrease in left atrial pressure (the sensor of the low-pressure vascular system). This "unloads" the left atrial mechanoreceptors, which in turn discharge into afferent vagal fibers that have appropriate central nervous system representation. As a consequence, efferent renal sympathetic nerve activity is augmented (54,55,57). Such an increase in sympathetic tone would tend to produce renal vasoconstriction and decrease GFR.

Although these theoretical considerations suggest a role for the sympathetic nervous system in the renal vasoconstriction and sodium retention of cirrhosis, only recently have studies been conducted to test this possibility. Studies to assess the activity of the sympathetic nervous system in cirrhotic humans have measured plasma catecholamine levels during basal conditions and after postural manipulations (55,57–62). Most observers agree that mean peripheral NE levels are elevated in cirrhotic patients (59–62); Ring-Larsen et al. (59) have determined plasma NE and epinephrine concentrations in differing vascular beds of cirrhotic patients at the time of hepatic venous catheterization. On the basis of differences in regional NE levels, they concluded that the elevated NE levels in patients with cirrhosis were attributable to enhanced sympathetic nervous system activity rather than to decreased metabolism.
As detailed in several recent reviews (63–65), however, the plasma concentrations of NE are an inadequate guide to either total or regional sympathetic activity. Global measures of sympathetic activity, such as plasma NE measurements, fail to identify sources of NE release and cannot delineate regional patterns of sympathetic nervous activation. Recently, Esler et al. (65) have conducted a physiologic and biochemical evaluation of patients with cirrhosis, applying tracer kinetic techniques using radiolabeled NE, thereby allowing a more precise description of the regional pattern of the sympathetic nervous derangement in cirrhosis. They demonstrated that the elevated plasma NE concentration in patients with cirrhosis is attributable to higher overall rates of spillover of the neurotransmitter to plasma and not to reduced plasma clearance caused by liver disease. The administration of clonidine reduced previously elevated NE overflow rates for the whole body including kidneys, and hepatomesenteric circulation. This sympathetic inhibition was accompanied by several potentially clinically beneficial effects: the lowering of renal vascular resistance, an augmentation of GFR, and the reduction of portal venous pressure (65).

In summary, the available data indicate that the sympathetic nervous system is activated in cirrhosis, both in the kidney and in other regional vascular beds, consequently contributing to the renal vasoconstriction and sodium retention of cirrhosis (57,65).

**Endotoxins.** Systemic endotoxemia may participate in the pathogenesis of the renal failure of cirrhosis. Endotoxins, the lipopolysaccharide constituents of the cell wall of certain bacteria, are potent renal vasoconstrictors (66). It has been hypothesized that enteric endotoxin is liberated into the systemic circulation through naturally or surgically created portosystemic shunts, thus bypassing the hepatic Kupffer cells, the major site of endotoxin removal. Recent studies have measured endotoxin by the limulus lysate technique and have reported that endotoxin is present in the portal and systemic circulation of many cirrhotic patients, particularly those with ascites. Because several investigators have demonstrated a high frequency of positive limulus assays in cirrhotic patients with renal failure but not in those without renal failure, endotoxins may contribute to the pathogenesis of the renal failure. Endotoxemia is appealing as a possible humoral agent not only because it may cause renal vasoconstriction, but also because it may produce vasodilation in other circulatory beds and may be a treatable condition (66,67). Indeed, Vallance and Moncada (see reference 72) have proposed that endotoxemia induces nitric oxide synthase in peripheral blood vessels with resultant vasodilation (vide infra).

Although endotoxemia is frequently observed in patients with chronic liver disease, its role in contributing to the development of renal failure is unclear. Attempts to correlate the occurrence of renal failure with the presence of endotoxemia are conflicting. On the one hand, Clemente et al. (68) observed endotoxemia in 9 of 22 patients with HRS, but not in cirrhotic patients with a normal GFR. On the other hand, Gatta et al. (69) demonstrated that in patients with cirrhosis without overt renal failure, renal vasoconstriction did not seem to be related to endotoxemia.

Coratelli et al. (70) have observed two patients before and after the development of HRS and demonstrated the appearance of endotoxemia coincident with the development of HRS.

Despite the ostensibly appeal of this hypothesis, much additional study is required for its confirmation. As has been pointed out in several reviews (66,67), the limulus tests for endotoxin have variations, and their individual accuracy is controversial. A correlation with renal failure in cirrhosis may reflect the retention of endotoxins rather than a causal relationship of endotoxins to HRS (67).

NO. A more recent approach to the investigation of the pathogenesis of the HRS has focused on the florid systemic hemodynamic disturbances that invariably accompany the syndrome. These include a hyperdynamic circulation, increased heart rate and cardiac output, and decreased blood pressure and systemic vascular resistance (4,20–22). These observations have suggested the likelihood of excess production of a vasodilator (71). A number of vasodilators have been postulated, including prostacyclin, bradykinin, substance P, and atrial natriuretic peptide, but clear evidence of involvement of any of them is lacking (4,71).

Recently, attention has focused on the role of NO as a mediator of both the hyperdynamic circulation and renal failure (72). NO, a vasodilator synthesized from L-arginine, accounts for the biologic activity of endothellium-derived relaxing factor (73,74). In animals, the agonist-induced release of NO from the vascular endothelium leads to peripheral vasodilation, a fall in blood pressure, and tachycardia (75,76). These effects are short lived, however, and vascular tone returns to normal once the agonist infusion is stopped. On the other hand, there is a second, distinct, inducible NO synthase that occurs in response to bacterial lipopolysaccharide endotoxin (77). Once induced, this enzyme releases NO for many hours without the need for further stimulation.

The in vitro incubation of vascular rings with endotoxin or cytokines leads to the induction of NO synthase in both the endothelium and the smooth muscle and to progressive vascular relaxation with diminished responsiveness to vasoconstrictors (78,79). When induced by endotoxin, these effects can be prevented by cycloheximide (an inhibitor of protein
synthesis), polymyxin B (an antagonist of endotoxin), and \( N^0 \)-monomethyl-L-arginine (an inhibitor of NO synthase) (77,78). Once NO synthase is induced and the vascular rings are relaxed, however, only \( N^0 \)-monomethyl-L-arginine will reverse these changes (78). On the basis of these considerations, Vallance and Moncada (72) have postulated that endotoxemia induces a NO synthase in peripheral blood vessels and that this increased NO synthesis and release accounts for the associated hyperdynamic circulation. If this hypothesis is correct, the inhibition of NO synthesis should restore sensitivity to vasoconstrictors and reverse these hemodynamic abnormalities. Specific inhibitors of either the constitutive or the inducible NO synthase theoretically should facilitate a more precise manipulation of NO synthesis and help to establish the pathophysiologic importance of NO in endotoxemia and cirrhosis.

In a recent preliminary communication, those investigators reported that serum nitrite and nitrate levels, an index of NO production, were elevated in a group of cirrhotic patients (80). The patients with ascites manifested higher nitrite and nitrate levels than did cirrhotic patients without ascites. Furthermore, there was a direct correlation between serum nitrite and nitrate levels and endotoxemia. Additional studies will be required to substantiate this hypothesis.

**Endothelin.** Recently, Moore et al. (81) have suggested the possibility that alterations in endothelin may play a pathogenetic role in the renal failure of the HRS. They reported that patients with the HRS had markedly elevated plasma endothelin-1 and endothelin-3 concentrations compared with normal subjects, patients having acute or chronic renal failure, and patients with liver disease without renal dysfunction. Those investigators interpreted their results to support the hypothesis that these substances play a role in the pathogenesis of the HRS. As I have noted in a recent editorial, it is equally possible if not probable that the results merely represent pari passu events (82). Thus, elevated plasma endothelin concentrations might be attributable to decreased renal disposal of endothelin. Additional studies are required to assess further the pathogenetic role of endothelin concentrations in this syndrome.

Moller et al. (81a) confirmed and extended these earlier observations. They characterized concentrations of endothelin-1 in various vascular beds including the hepatic artery/vein, the right renal artery/vein, and the right femoral artery/vein and related the findings to clinical status and hemodynamic alterations. Median brachial venous endothelin-1 concentrations were substantially higher in patients with cirrhosis (3.40 pg/mL; range, 1.25 to 7.84; \( N = 24 \)) than in controls (1.53 pg/mL; range, 0.78 to 2.12; \( N = 11 \) \( P < 0.00005 \)). In patients with cirrhosis, ET-1 was directly correlated to serum creatinine \( (r = -0.58; \ P < 0.003) \). In patients who underwent liver vein catheterization \( (N = 8) \), no significant differences were found in endothelin-1 plasma concentrations between the liver, renal, or femoral veins on the one hand and the femoral artery on the other \( (P > 0.1) \), indicating no major net elimination or release in the liver, kidney, or lower limb.

**Role of Biologically Active Atrial Peptides.** Another hormone that should be included in any consideration of the pathogenetic mechanisms of HRS is atrial natriuretic factor (ANF) or atriopeptin. Since the demonstration by DeBold et al. (83) in 1981 that saline extracts of rat heart atria, but not ventricles, caused a marked natriuresis and diuresis when injected into normal rats, there has been much interest in the role of ANF as a mediator of volume homeostasis. Micropuncture studies in rats have shown that ANF, given by either bolus injection or continuous infusion, causes a significant increase in GFR (84,85), as well as natriuresis and diuresis (86).

Because ANF has thus been shown to be of importance in volume homeostasis and because volume homeostasis is of critical importance in patients with cirrhosis and portal hypertension, a number of investigators have sought a role for ANF in severe hepatic disease.

Despite proposals that ANF deficiency may contribute to the renal dysfunction of liver disease, the available data fail to support this formulation. Most investigators have found immunoreactive ANF levels in plasma to be either normal (87,88) or increased (89,90) in cirrhotic patients with ascites. Morgan et al. (91) compared circulating ANF levels in seven patients with HRS and seven patients with advanced alcoholic liver disease and ascites but normal serum creatinine levels. They demonstrated that ANF levels were twofold higher in the patients with HRS, indicating that a deficiency of ANF does not contribute to the renal failure.

**ACUTE RENAL FAILURE (ATN)**

Although much attention has been directed to HRS, it should be borne in mind that cirrhotic patients are as vulnerable as noncirrhotic patients to the development of ATN. Among liver disease patients in whom renal failure developed, the etiology of renal failure is more commonly ATN than HRS (1–4). The increased frequency of ATN may relate to the hypotension, bleeding dyscrasias, infection, and multiple metabolic disorders that complicate the clinical course of these patients. There have been several attempts to develop diagnostic tests to reliably discriminate between acute renal failure and HRS (92–96). To date, these tests, which rely on enzymuria or...
Hepatorenal Syndrome

electrolyte excretory patterns, are often suggestive but lack sufficient selectivity to be reliable.

HRS Versus ATN: Different Diseases or a Continuum?

Renal function in HRS is fundamentally different from that in ATN. In ATN, the reduction in GFR is generally much more severe, and the accompanying decrease in tubular reabsorption is generally regarded as evidence of intrinsic tubular dysfunction. In HRS, on the other hand, the reduction in GFR is usually not as severe, and the avid tubular reabsorption of sodium and water attests to normal intrinsic tubular function, which appears to be responding to extrinsic stimuli.

It is immediately evident to the experienced clinician that "patients don’t necessarily read textbooks." Often, the urinary indices are confusing and fall in the "grey zone," which spans the different presentations of HRS and ATN (see Differential Diagnosis, below). Furthermore, patients with HRS often develop classic ATN as their condition deteriorates. Although rigorous data are lacking, I believe that the HRS can evolve into ATN, and in many cases, the natural history appears to be a continuum between the two. In terms of management, however, it is often confusing to be faced with a pattern of renal function that does not clearly fit into the categories outlined above. Under these circumstances, the only practical approach is to consider the patient as being "prerenal" and search diligently for the reversible causes of prerenal azotemia.

Differential Diagnosis

The abrupt onset of oliguria in a cirrhotic patient does not necessarily imply the presence of HRS. Pre-renal causes are important to differentiate, particularly because they constitute reversible conditions if recognized and treated in the incipient phase. Volume contraction or cardiac pump failure may appear as a "pseudohepatorenal" syndrome. Furthermore, as already emphasized, it is not uncommon for patients with alcoholic cirrhosis to develop classic acute renal failure (ATN). In many instances, the differentiation from HRS can be made readily by recognition of the precipitating event and by characteristic laboratory findings. Table 2 lists laboratory features that are helpful in differentiating the three principal causes of acute azotemia in patients with liver disease. The most uniform urinary finding of HRS patients is a strikingly low sodium concentration, usually less than 10 mEq/L and occasionally as low as 2 to 5 mEq/L. Unfortunately, prerenal azotemia is associated with similar low urinary sodium concentrations. In contrast, patients with oliguric ATN frequently have urinary sodium concentrations exceeding 30 mEq/L, and usually even higher.

Although avid renal sodium retention is evident in the majority of patients with HRS, occasional patients with HRS have been recognized in whom the urinary sodium concentration [UNa] is consistently greater than 10 mEq/L. In some of these patients, [UNa] is initially low but increases to levels of approximately 40 mEq/L as renal impairment progresses; it has been suggested that this late increase in urinary sodium concentration may represent the possible transition to ATN. Other patients have been recognized in whom HRS has developed and progressed in the presence of a [UNa] persistently in the range of 20 to 30 mEq/L (1,4).

Both HRS and prerenal azotemia manifest well-maintained urinary concentrating ability characterized by a urine-to-plasma osmolality ratio exceeding 1.0, whereas ATN patients excrete a relatively iso-osmotic urine (i.e., urine that is neither concentrated nor dilute). The urine-to-plasma creatinine ratio is greater than 30 (and at times 40:1) in both prerenal failure and HRS, whereas the urine-to-plasma creatinine ratio is 20:1 or less in ATN. Proteinuria is absent or minimal in HRS.

In summary, the finding of a low urinary sodium

<table>
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<tr>
<th>TABLE 2. Differential diagnosis of acute azotemia in the patient with liver disease: important differential urinary findings</th>
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<tr>
<td><strong>Prerenal Azotemia</strong></td>
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<tr>
<td><strong>Urine Sodium Concentration (mEq/L)</strong></td>
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<tr>
<td><strong>Urine-to-Plasma Creatinine Ratio</strong></td>
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<td><strong>Urine Osmolality</strong></td>
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<td><strong>Urine Sediment</strong></td>
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<sup>a</sup>The numbers cited in the table are arbitrary and are meant to highlight the salient differences in these three diagnostic categories. However, the values vary. As an example, UNa occasionally may exceed 10 mEq/L.

<sup>b</sup>Radiocontrast agents and sepsis may lower urinary sodium concentration in the patient with ATN. When urinary output is very low, the concentration of sodium may rise. Urinary sodium levels may also rise when vasoconstriction is so severe that ATN sets in.
concentration in the presence of oliguric acute renal failure usually precludes the diagnosis of ATN. Only when prerenal failure and ATN are excluded can one establish the diagnosis of HRS.

TREATMENT

General Considerations

The management of the HRS has been discouraging in view of the absence of any reproducible, effective treatment modality. Because knowledge about the pathogenesis of HRS is inferential and incomplete, therapy to this time has been supportive. Because iatrogenic events often precipitate this syndrome and because therapy is difficult once the syndrome is established, prevention constitutes the linchpin of management.

The initial step in the management of a cirrhotic patient with acutely reduced renal function is to not equate decreased renal function with HRS, but rather to search diligently for and treat correctable causes of azotemia such as volume contraction, cardiac decompensation, and urinary tract obstruction. The diagnosis of ATN (acute intrinsic renal failure) should clearly be considered because ATN occurs commonly in cirrhotic patients and they may be expected to recover if supported with dialytic therapy.

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DIALYSIS

Dialysis was previously reported to be ineffective in the management of HRS (103,104). Our own recent experience, however, suggests that such a sweeping condemnation should be qualified (105). Although most of the published literature indeed suggests a dismal prognosis for patients who are dialyzed, such early reports have dealt with patients with chronic end-stage liver disease. In a few instances, we have undertaken dialysis in HRS patients with acute hepatic disease and have been gratified by the ultimate favorable outcome. Our experience suggests that in selected patients, i.e., those with acute hepatic dysfunction in whom there is reason to believe that the renal failure may reverse coincident with the resolution of the acute hepatic insult, dialytic therapy is indicated.

With the recent maturation and refinement of orthotopic liver transplantation and its acceptance as the treatment of choice for end-stage liver disease, dialysis has assumed an important ancillary role. Dialysis is now widely used as a supportive measure in the management of many patients awaiting liver transplantation.

In addition to stabilizing renal function, it is often necessary to remove fluid, either to prevent life-threatening emergencies such as acute pulmonary edema or to permit the administration of requisite fluids such as bicarbonate solutions or hyperalimentation. Although hemodialysis often constitutes the therapeutic modality of choice for this purpose, it is not feasible in many patients with severe liver disease who have associated hemodynamic instability. Unfortunately, patients with decompensated cirrhosis frequently become hypotensive in response to the institution of hemodialysis. To circumvent this problem, we have used continuous arteriovenous hemofiltration as an alternative maneuver in a few patients with HRS and have been successful in mobilizing fluid without concomitant hemodynamic instability (106,107). Additional experience will be required to clarify the role of this approach in managing patients with HRS.

Peritoneovenous (LeVeen) Shunt

An advance that has engendered major controversy in the management of HRS is the development of peritoneovenous (PV) shunting (108-111). The past 20 yr have witnessed a flurry of enthusiasm for the use of PV (LeVeen) shunting in the management of HRS. Because the underlying abnormality is thought to be a maldistribution of extracellular fluid with a resultant diminished effective blood volume, attention has focused on developing procedures to redistribute body fluids between compartments, so that the central compartment is replenished despite decreasing ascites. Unfortunately, although there have been a few well-documented "successes" (109,111), the majority of reports have been anecdotal with insufficient details to allow critical assessment. Even where sufficient data were available, we must conclude that the majority of putative "successes" occurred in patients who were not clearly documented to have HRS; rather, many patients probably had reversible azotemia secondary to a diminished effective blood volume (110,111).

Only two prospective, randomized studies of the role of the PVS in the treatment of HRS have been performed (112,113). Linas et al. (112) prospectively compared the effects of the PV shunting (N = 10) or medical therapy (N = 10) on renal function and mortality in 20 patients with the HRS associated with alcoholic liver disease. After 48 to 72 h, body weight and serum creatinine were increased with medical therapy and decreased (from 3.6 ± 0.4 to 3.0 ± 0.5 mg/dL; P < 0.05) in patients with the shunt. Despite the improvement of renal function, only one patient with the PVS had a prolonged survival (210 days). In the remainder, survival was 13.8 ± 2.2 days compared with 4.1 ± 0.6 days with medical therapy. The investigators concluded that, whereas PV shunting often stabilizes renal function, it does not prolong life in patients with the HRS. Additional studies are currently under way in HRS patients with less advanced disease.

In the VA Cooperative Study (113), although there were 7 long-term survivors in a group of 14 patients treated with PVS, the results were not statistically significant when compared with those of a group of 19 patients undergoing medical therapy. The mean half-life of patients treated with the shunt did not differ significantly from that of controls. Of note, the group of patients with the HRS was carefully selected, and patients with severe complications of chronic liver disease were excluded.

On the basis of the available data, it is apparent that a beneficial role for the PVS in the treatment of the HRS has not been established. Although some patients exhibit an improvement in renal function, further controlled studies, with larger number of patients, are necessary to delineate the effect of the PVS on long-term survival, quality of life, and the incidence of complications.

Orthotopic Liver Transplantation. Orthotopic liver transplantation (OLTx) has recently become the accepted treatment for end-stage liver disease (114). Of interest, many of these patients are admitted with varying degrees of concomitant renal dysfunction, including the HRS. OLTx has been reported to reverse HRS acutely (11.115,116). Recently, Gonwa et al. (114) reviewed the extensive experience of the Baylor University transplant group and have reported...
a good, long-term survival with return of acceptable renal function for prolonged periods. They retrospectively reviewed the first 308 patients undergoing OLTX. The incidence of HRS was 10.5%. HRS patients manifested an increase in GFR from a baseline of $20 \pm 4$ mL/min to a mean of $33 \pm 3$ mL/min at 6 wk, with a further increase to $46 \pm 6$ mL/min at 1 yr. GFR remained stable at 2 yr postoperatively ($38 \pm 6$ mL/min). There was no difference in perioperative (90-day) mortality between HRS and non-HRS patients, despite a worse preoperative status and a more unstable postoperative course. The actuarial 1- and 2-yr survival rate for the HRS patients was 77%, not different from that of non-HRS patients. These investigators concluded that with aggressive pretransplant and posttransplant management, one can anticipate excellent results after OLTX in patients with the HRS.

**Newer Experimental Modalities.** As noted previously, nonsteroidal anti-inflammatory drugs have been shown to induce reversible decrements in renal perfusion and renal function in patients with decompensated cirrhosis (40–43). Conversely, we have shown that the augmentation of renal prostaglandins induced by water immersion is associated with marked increments in creatinine clearance (44,45). The infusion of vasodilator prostaglandins to correct a possible renal prostaglandin deficiency has been unrewarding (38). The widest experience has been with PGA and PGE. Although such therapeutic manipulations have occasionally resulted in salutary effects on renal function, the benefits have not been sustained.

Feverly et al. (117) have recently attempted to extend these observations by investigating the effects of the administration of a PGE1 analog (misoprostol) on renal function in four patients with alcoholic cirrhosis and HRS. In response to misoprostol administration (0.4 mg orally four times daily) and albumin infusions, urine volume increased threefold to fourfold. Concomitantly, serum creatinine levels diminished. All patients had hyponatremia, which normalized with misoprostol administration. Although the experience is preliminary, it raises the possibility that the provision of exogenous prostaglandins may have a salutary role in the management of the HRS. Our initial enthusiasm must be tempered, however, by the subsequent failure of these investigators, or other groups, to confirm these initial observations.

**TX Inhibitors.** As detailed above (p. 7), several investigators have proposed that alterations of TX may contribute to the development of renal dysfunction (48,50,52). Consequently, there have been attempts to modify the course of the HRS by the administration of selective inhibitors of TX synthesis (50,51). Whereas nonspecific cyclo-oxygenase inhibitors, such as indomethacin and aspirin, reduce both TX and prostaglandin synthesis to varying degrees in different biologic systems, selective inhibitors of TX synthesis preserve or possibly increase the production of other metabolites of arachidonic acid, such as the potent vasodilator prostacyclin. Zipser et al. (50) administered the TX synthetase inhibitor dazoxiben to patients with alcoholic hepatitis and progressive azotemia. Although the administration of dazoxiben reduced the urinary excretion of the TX metabolite TxB2 by approximately 50%, PGE2 and 6-keto-PGF1α excretion was essentially unaltered. Despite the reduction in TX excretion, there was no consistent reversal of the progressive renal deterioration (50).

Gentilini et al. (51) also investigated the effects of a TX synthase inhibitor in cirrhotic patients. They administered OKY 046, a selective TxA2 synthase inhibitor, 200 mg thrice daily for 5 days, to nine nonazotemic cirrhotic patients with ascites and avid sodium retention. OKY 046 increased inulin clearance by 19%, whereas RBF was unchanged. Drug administration did not alter the avid sodium retention and did not affect PRA or the plasma aldosterone level.

Unfortunately, the administration of TX synthase inhibitors is associated with a number of confounding factors that render the results difficult to interpret. Indeed, these drugs may lead to the accumulation of the prostaglandin endoperoxides PGG2 and PGH2, which mimic the renal effects of TxA2 by interacting with the same receptors. As an example, arachidonic acid–induced vasoconstriction in the rat kidney is only partially reduced by pretreatment with a TX synthase inhibitor, whereas it is completely abolished by the administration of a TX receptor antagonist (118).

In an attempt to obviate these problems, Laffi et al. (52) have recently conducted a randomized, double-blind, crossover trial to characterize the effects of the TX receptor antagonist ONO-3708 on renal hemodynamics and excretory function in 15 nonazotemic cirrhotic patients with ascites. Urinary TxB2 excretion was threefold higher than in healthy subjects. The administration of ONO-3708 significantly blocked TxA2 receptors; bleeding time showed a twofold increase, and platelet aggregation to the TX receptor agonist U-46619 was abolished in all patients studied. ONO-3708 induced an 86% increase in free water clearance compared with placebo ($P < 0.001$), which was associated with a significant diuresis. RPF, as measured by p-aminohippurate clearance, increased 14% during TX receptor blockade ($P < 0.05$), whereas GFR, as assessed by inulin, was unchanged. Additional studies with TX receptor antagonists in patients with widely varying degrees of acute renal insufficiency will be required to further define the possible utility of these agents in the treatment of the HRS.
Other Treatment Modalities

In view of the prominent role assigned to renal cortical ischemia in the pathogenesis of HRS, it is not altogether surprising that there have been numerous attempts to treat HRS with vasodilators. The intrarenal infusion of nonspecific vasodilators such as acetylcholine and papaverine improve RBF but do not augment GFR (119). Similarly, the blockade of vasoconstrictor α-adrenergic nerves by the intrarenal infusion of phentolamine or phenoxybenzamine or the stimulation of vasodilator β-adrenergic nerves with isoproterenol has no significant effect on GFR (13).

The direct stimulation of renal dopaminergic receptors by the infusion of nonpressor doses of dopamine produces renal vasodilation, but again, GFR and urine flow are virtually unaffected, despite infusions for as long as 24 h (29, 120, 121).

Finally, a variety of other treatment modalities have been proposed, including prednisone, exchange transfusion, charcoal hemoperfusion, xenobiotic cross-circulation, and ex vivo baboon liver perfusion (4, 122). None are of demonstrated benefit, and the actual and potential complications are of sufficient magnitude to dictate great hesitation in their clinical use.

Water Immersion

We are often asked in consultation if water immersion might be tried as a therapeutic maneuver for a patient who has been diagnosed as having the HRS. As noted above, there has been an increasing awareness that the underlying abnormality in patients with decompensated cirrhosis is not solely an excess of total body fluid, but is to a greater extent a maldistribution of extracellular fluid. Consequently, much attention has been focused on developing procedures to redistribute body fluids, not only between compartments, as with the PVS, but also within the vascular compartment.

Studies from our laboratory have provided substantial evidence that head-out water immersion markedly augments central blood volume (56, 123). To the extent that diminished effective blood volume constitutes a major determinant of renal sodium retention in established liver disease, one might justifiably speculate on the use of water immersion as a means of replenishing the contracted effective volume. Although at first glance such a proposal appears attractive, several arguments have been marshaled against this approach. (1) The repeated use of water immersion would be a time-consuming and costly procedure requiring the continuous attendance of paramedical personnel. (2) These patients are clinically fragile, and exposure to the marked hemodynamic alterations that attend immersion requires close medical monitoring. (3) Finally, a patient could only reasonably be immersed for a small percentage of the day, and it is unknown if this confers a lasting beneficial effect.

The long-term effect of water immersion on central blood volume is unknown. Certainly, water immersion constitutes a powerful and highly productive means of investigating deranged volume homeostasis in many edematous disorders, especially cirrhosis (14, 17, 27, 45). We believe, however, that at this time, pending carefully controlled investigative pilot studies, immersion should not be used uniformly as therapy in managing patients with decompensated cirrhosis.

Considerations for Future Therapeutic Approaches

An additional investigative approach that has not been undertaken but that merits consideration is the possible role of calcium antagonists. Studies from several laboratories, including our own, have demonstrated profound effects of these calcium antagonists on renal vascular smooth muscle and concomitant alterations in renal function (124, 125). Specifically, calcium antagonists have been shown to augment and restore GFR in diverse experimental settings characterized by renal vasoconstriction. This effect is due, in part, to the selective reduction of afferent arteriolar resistance. In essence, calcium antagonists may constitute selective renal vasodilators that reverse or attenuate renal ischemia (126). Indeed, studies from several laboratories have recently demonstrated that calcium antagonists are effective in the prophylaxis of acute renal insufficiency in diverse clinical settings, including cadaveric kidney transplantation and radiocontrast-induced renal dysfunction (126). Because patients with HRS manifest a more extreme degree of preferential renal cortical ischemia, it appears reasonable to anticipate that calcium antagonists can induce a similar salutary effect on renal hemodynamics. If it can be demonstrated that calcium antagonists can be safely administered to patients with decompensated cirrhosis without inducing concomitant hypotension, they may constitute an additional therapeutic approach to the management of the HRS.

Vasoconstrictor Therapy. A final therapeutic approach that warrants consideration is the administration of vasoactive agents that preferentially reverse the decreased systemic vascular resistance without increasing renal vascular resistance. As discussed previously (21, 127), there has been a resurgence of interest in the role of peripheral vasodilation as the primary determinant of intravascular underfilling. The resultant imbalance between the ex-
panded capacitance and the available volume eventuates in a diminished effective volume. Such a formulation dictates that therapy should be directed toward a correction of the diminished systemic vascular resistance in HRS patients. Such an approach is not novel. Thirty years ago, Gornel et al. (128) demonstrated that the administration of the pressor amine metaraminol in cirrhotic patients is often followed by an increase in GFR, an increase in urine flow, and the elaboration of a more dilute urine. Although the use of metaraminol was fraught with problems, it would appear that the general approach of administering pressor agents might be valid.

Twenty-five years ago, Cohn et al. (129) demonstrated that a synthetic analog of lysine vasopressin (octapressin; PLV-2) had the unique property of producing renal vasodilation combined with systemic vasoconstriction, thereby producing a redistribution of blood flow to the kidney. Those investigators studied the systemic and renal hemodynamic effects of PLV-2 in patients with decompensated cirrhosis of the liver. Low doses (0.004 to 0.02 U/min) increased RBF (indicator-dilution technique), reduced renal vascular resistance, and produced a slight increase in arterial pressure and systemic vascular resistance. The fraction of the cardiac output delivered to the kidney was increased at all dose levels. The increased RBF was accompanied by a more rapid intrarenal dye transit time and a slight increase in the renal extraction ratio of p-aminophippurate, suggesting a rise in cortical blood flow. They concluded that PLV-2 in small doses produced renal vasodilation, and in larger doses, it produced preferential extrarenal vasocostriction, resulting in a redistribution of blood flow to the kidney. On the basis of these findings, Cohn et al. (129) proposed a possible role for PLV-2 in the management of HRS. Unfortunately, additional studies were not undertaken.

Recently, there has been renewed interest in the hemodynamic derangements and attempts to improve renal function by countervailing this hyperdynamic state. Lenz et al. (130) investigated the effects of the infusion of ornipressin on renal and circulatory function. In a preliminary report, they observed that ornipressin reversed the hyperdynamic state. Concomitantly, there was improvement in renal function, as assessed by a more than 70% increase in creatinine clearance and a doubling in urine flow. These preliminary observations lend support to the concept that the peripheral vasodilation of liver disease contributes importantly to the renal dysfunction. Consequently, maneuvers that counter the vasodilation may possibly prove to be of benefit in improving renal function. In this regard, clinical trials attempting to reverse the HRS should be undertaken with additional vasoactive agents that selectively increase systemic vascular resistance.

SUMMARY

In summary, despite considerable progress in the past three decades, we still lack a comprehensive understanding of the pathogenetic cascade that produces HRS. Although there has been some progress in characterizing the pathogenesis of this condition, therapy is largely empirical. Much progress in the delineation of the intrarenal hemodynamic alterations that underlie the HRS has been witnessed in the past two decades. The numerous attempts at treating HRS empirically with vasodilators have not resulted in important therapeutic innovations. The failure of many HRS patients to survive despite partial correction of their renal hemodynamic abnormality is a reflection of the precarious state of the patient with liver failure. Hemorrhage, infection, and hepatic coma are the usual causes of death in these patients.

It is apparent that any future breakthroughs in providing definitive treatment of HRS must be predicated on a greater clarification of the mechanisms and a delineation of the mediators. The role of hemodialysis has recently undergone reappraisal, and it is apparent that dialysis clearly has a role in supporting patients awaiting hepatic transplantation. Dialysis also may be warranted as a supportive measure in some patients with apparently reversible hepatic dysfunction. Hepatic transplantation has evolved over the past decade to the point where it constitutes definitive therapy for patients with hepatic dysfunction and concomitant renal failure. Although anecdotal information suggests that PV shunting has a role in the management of select patients with HRS, the results of available prospective studies have failed to confirm such approach. Finally, the advent of the peripheral vasodilation theory and its focus on the generalized hemodynamic perturbations in the patient with the HRS have re-focused attention on the florid extrarenal hemodynamic derangements. This suggests that pharmacologic interventions that counter the peripheral vasodilation may afford benefit with regard to both systemic hemodynamics and renal function. It is hoped that future clinical trials will establish the precise contribution of each of these treatment modalities and its respective role in the therapeutic armamentarium.

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