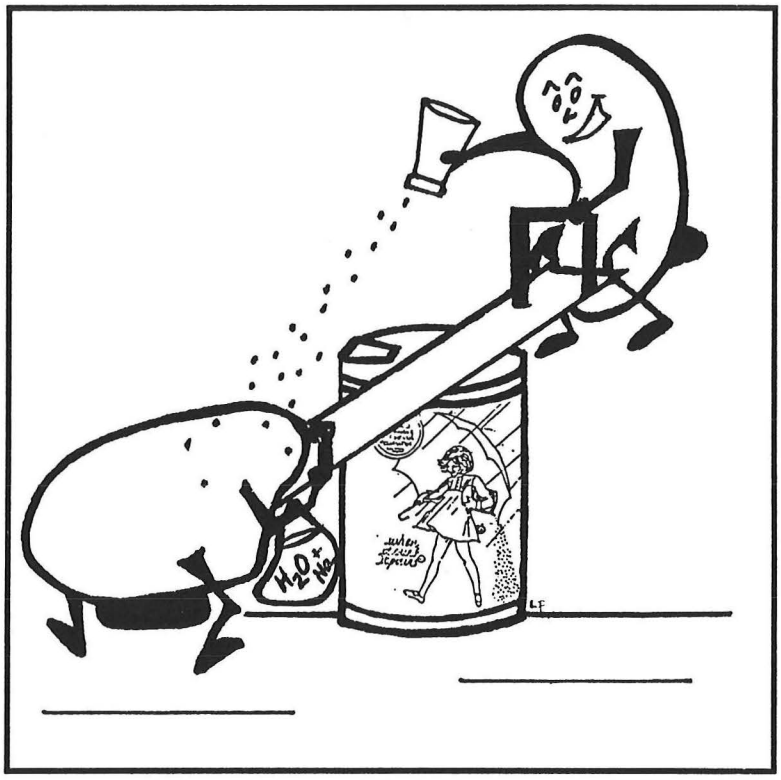
PATHOGENESIS OF ASCITES AND EDEMA FORMATION IN CIRRHOSIS:

A Renal Balancing Act



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I. Introduction

Renal sodium excretion is normally regulated so that extracellular fluid (ECF) volume is maintained within normal limits. Any maneuver that increases ECF volume will lead to a prompt and sustained natriuresis until the volume returns to normal. In patients with cirrhosis, this homeostatic mechanism becomes deranged such that large increases in ECF volume are accompanied by continued renal salt retention resulting in edema and ascites formation. This grand rounds will discuss the pathogenesis of ascites and edema formation in chronic liver disease. Implications for treatment will also be discussed.

II. Presinusoidal versus Postsinusoidal Obstruction and Ascites Formation

In patients with cirrhosis, the kidneys are normal but are signaled to retain salt in an unrelenting manner. The critical event in the generation of this signal is development of hepatic venous outflow obstruction. In the normal state, the portal circulation is characterized by high flow, low pressure, and low resistance. The imposition of a resistance into this high-flow vasculature will uniformly raise portal pressure, but development of ascites is critically dependent on location of the resistance. Conditions associated with presinusoidal vascular obstruction such as portal vein thrombosis and schistosomiasis raise portal pressure but are not generally associated with ascites. By contrast, hepatic diseases such as Laennec's cirrhosis and Budd-Chiari syndrome cause early postsinusoidal vascular obstruction and are associated with marked degrees of salt retention, anasarca, and ascites. Thus, during the development of the cirrhotic process, ascites will accumulate primarily when the pathologic process is associated with hepatic venous outflow obstruction and sinusoidal hypertension.

This distinction between presinusoidal and postsinusoidal obstruction can best be explained by comparing the characteristics of fluid exchange in capillaries of the splanchnic bed versus those in the hepatic sinusoids. The intestinal capillaries are similar to those in the peripheral tissues in that they have continuous membranes with small pores such that a barrier exists preventing plasma proteins from moving into the interstitial space. An increase in capillary hydrostatic pressure will cause the movement of a protein poor fluid to enter the interstitial compartment and decrease the interstitial protein concentration (1). Interstitial protein concentration is further reduced by an acceleration in lymph flow that is stimulated by the fluid movement. As a result, the interstitial oncotic pressure falls while the plasma oncotic pressure remains unchanged. The net oncotic force therefore rises and offsets the increase in hydrostatic force providing a buffer against excessive fluid filtration. The fall in protein concentration is maximal in intestinal lymph at relatively low pressures and is much greater than that observed from the cirrhotic liver (2). The protein content of splanchnic lymph measured in human cirrhotics is approximately 18% of the plasma protein concentration (3). Thus, the increase in net oncotic force associated with dilution of the interstitial protein and accelerated lymph flow contribute to the protection against ascites in patients whose only abnormality is portal hypertension.

The situation across the liver sinusoids is quite different. Hepatic sinusoids, unlike capillaries elsewhere in the body, are extremely permeable to protein. As a result, colloid osmotic pressure exerts little influence on movement of fluid. Rather, direction of fluid movement is determined almost entirely by changes in sinusoidal hydraulic pressure. Thus efflux of protein-rich filtrate into the space of Disse is critically dependent on hepatic venous pressures. Obstruction to hepatic venous outflow will lead to large increments in formation of hepatic lymph and flow

through the thoracic duct. Unlike the intestinal capillaries, there is little to no restriction in the movement of protein into the interstitium such that the protein concentration of hepatic lymph will quickly approach that of plasma (4). As a result there is no oncotic gradient between plasma and interstitium at high sinusoidal pressures and flow. The formation of lymph can be more than 20-fold greater in cirrhosis as compared to a normal liver (3). The predominance of hepatically produced lymph to overall lymph production is illustrated by studies in experimental animals with cirrhosis. Barrowman et al., found a 29-fold increase in hepatic lymph flow while only a 3-fold increase was noted in the splanchnic lymphatics (2). Eleven of 19 animals had normal flows of intestinal lymph while all the cirrhotic animals had increased flows in liver lymph. Whereas in normal humans 1-1.5 liters/day of lymph are returned to the circulation, subjects with cirrhosis even without ascites may have lymph flow through the thoracic duct as high as 15-20 liters/day (5). When sinusoidal pressure increases to such a degree that hepatic lymph formation exceeds the capacity of the thoracic duct to return fluid to the circulation, interstitial fluid weeps off the liver into the peritoneal space and forms ascites (6).

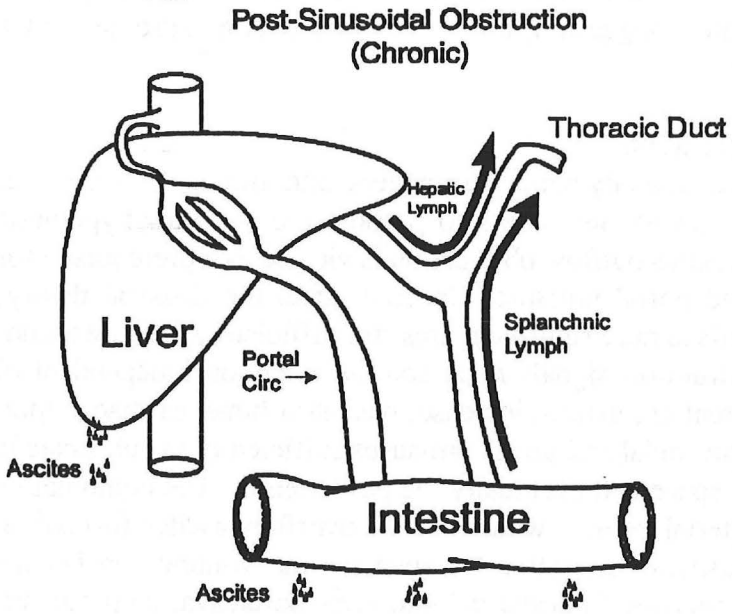
Conditions associated with the rapid onset of postsinusoidal obstruction such as acute right sided congestive heart failure and Budd Chiari syndrome initially give rise to ascitic fluid that has a high protein concentration that may even approach that of plasma. This high protein concentration is reflective of the liver being the predominant source of the ascitic fluid. However, over time the protein content of ascites in these conditions begins to decrease. Witte et al., measured the total protein in ascitic, pleural, and peripheral edema fluid in acute and chronic heart failure patients (7). In the setting of acute heart failure the mean concentration of protein in ascitic fluid was approximately 5 g/dl. By contrast, the protein concentration in ascitic fluid of chronic congestive heart failure patients was 2.7 g/dl. A lower protein concentration is also typical of conditions such as Laennec's cirrhosis in which post sinusoidal obstruction develops slowly.

Two phenomena contribute to this change in ascitic fluid protein concentration. If the hepatic sinusoids are subjected to an increased hydrostatic pressure for a long period of time they begin to assume the anatomic and functional characteristics of capillaries found elsewhere in the body, a process referred to as capillarization (8). This change leads to a decrease in albumin permeability such that oncotic forces begin to play some role in hepatic lymph formation. At the same time hypoalbuminemia develops secondary to decreased hepatic synthesis as well as dilution secondary to ECF volume expansion. As a result, the protein content of hepatic lymph while still high falls to approximately 50-55% of plasma values (3).

The second factor contributing to the lower ascitic protein concentration is the superimposition of portal hypertension. Early in the development of portal hypertension when plasma protein concentration is normal only minimal amounts of ascitic fluid is generated in the splanchnic bed due to the buffering effect of increased net oncotic force opposing fluid filtration. Extremely high hydrostatic pressures are required to produce significant amounts of ascitic fluid in the setting of normal plasma protein concentrations. By contrast, less and less hydrostatic pressure is required for the formation of ascitic fluid as the plasma albumin concentration decreases and the net osmotic force declines (9). In this setting large amounts of ascitic fluid characterized by a low protein concentration is generated in the splanchnic capillary bed. Ascites develops when the production of lymph from either or both the hepatic sinusoids and the splanchnic circulation exceeds the transport capacity of the lymphatics. The final protein concentration measured in the peritoneal fluid is determined by the sum of the two contributing pools of fluid; one relatively high in protein originating in the liver and the other, a low protein

filtered across splanchnic capillaries.

The development of portal hypertension in association with chronic liver disease is accompanied by profound changes in the splanchnic circulation that secondarily lead to increased lymph production in the splanchnic bed. The importance of the splanchnic lymphatic pool in the generation of ascites is reflected by the fact that in most instances ascitic fluid is transudative and characterized by a protein concentration of <2.5 g/dl. Classically, portal hypertension was considered to be the sole result of increased resistance to portal venous flow. However, studies in experimental models suggest that an increased portal venous inflow secondary to generalized splanchnic arteriolar vasodilation also plays a role in the genesis of increased portal pressure (10-12). This vasodilation leads to changes in the splanchnic microcirculation that may predispose to increased filtration of fluid. For example, an acute elevation of venous pressure in the intestine normally elicits a myogenic response that leads to a reduction in blood flow. This decrease in flow is thought to serve a protective role against the development of bowel edema. However, in chronic portal hypertension this myogenic response is no longer present. In this setting arteriolar resistance is reduced such that capillary pressure and filtration are increased (13). The loss of this autoregulatory mechanism may account for the greater increase in intestinal capillary pressure and lymph flow seen under conditions of chronic portal hypertension when compared to acute increases in portal pressure of the same magnitude (14). The potential causes of splanchnic arteriolar vasodilation is discussed below.



There are several observations that support an important role for portal hypertension in the pathogenesis of ascites. First, patients with ascites have significantly higher portal pressures as compared to those without ascites (15,16). Although the threshold for ascites development is not clearly defined it is unusual for ascites to develop with a pressure below 12 mm/Hg. Gines found that only 4 of 99 cirrhotic patients with ascites had a portal pressure <12 mm/Hg as estimated by hepatic venous wedged pressure (17). Second, portal pressure correlates inversely with urinary sodium excretion (16,18). Third, maneuvers designed to reduce portal pressure are known to have a favorable effect on the development of ascites. For example, surgical portosystemic shunts used in the treatment of variceal bleeding reduce portal pressure and are associated with a lower probability of developing ascites during follow up (19). Both side-to-side and end-to-side portocaval anastomosis have been shown effective in the management of refractory ascites in cirrhosis. Recent studies also suggest that reducing portal pressure with a transjugular intrahepatic portasystemic shunt has a beneficial effect on ascites (20).

III. Afferent Limb of Sodium Retention: Overfill Versus Underfill Mechanism

A. Classical Underfill Mechanism for Renal Salt Retention

The mechanism by which hepatic venous outflow obstruction leads to sufficiently high sinusoidal pressures for ascites formation is controversial. The classical (underfill) theory predicts that the degree of hepatic venous outflow obstruction is sufficient in the presence of normal splanchnic perfusion to perturb the balance between rates of hepatic lymph formation and thoracic duct flow, thereby resulting in formation of ascites. Both increased sinusoidal and portal venous pressures in conjunction with hypoalbuminemia cause formation of ascites in the presence of normal splanchnic perfusion. The formation of ascites, however, occurs at the expense of decreased intravascular volume. In consequence, a low venous filling pressure and a low cardiac output activate baroreceptor mechanisms, resulting in renal salt retention. According to this formulation, development of ascites is the primary event that leads to an underfilled circulation and subsequent renal salt retention. The failure of measured hemodynamic parameters to satisfy predictions of the classical theory has raised questions regarding its validity. As originally conceived, it was predicted that extrasplanchnic plasma volume would be decreased and that cardiac output would be low. When measured, however, these values have rarely been low (21,22). In fact, measurements have indicated that total plasma volume is usually elevated in cirrhotic patients. Similarly, cardiac output is rarely low but tends to vary from normal to very high. In addition, studies performed in animal models of cirrhosis have found that sodium retention precedes the formation of ascites, suggesting that salt retention is a cause and not a consequence of ascites formation.

B. Overfill Mechanism for Renal Salt Retention

The incompatibility of measured hemodynamic parameters and timing of renal salt retention with the classical theory of ascites has led others to propose the overflow hypothesis (23). Once again, hepatic disease with venous outflow obstruction is viewed as a prerequisite for development of increased sinusoidal and portal pressures. In contrast to the classical theory, however, normal splanchnic perfusion fails to raise sinusoidal pressure sufficiently to cause ascites formation. Rather, venous outflow obstruction signals renal sodium retention independent of diminished intravascular volume. Salt retention, in turn, increases plasma volume, cardiac output, and splanchnic perfusion, thus raising sinusoidal and portal pressures sufficiently to culminate in translocation of fluid into the interstitial space and eventually the peritoneum. The combination of portal hypertension and increased arterial volume would lead to overflow ascites formation. This hypothesis is supported by the positive correlation between plasma volume and hepatic venous pressure and the persistence of increased plasma volume after portacaval anastomosis. Moreover, patients with ascites have significantly higher portal pressure than patients without ascites, and portal pressure correlates inversely with urinary sodium excretion (17).

Additional evidence linking hepatic venous outflow obstruction directly to renal sodium retention comes from studies performed in dogs fed the potent hepatotoxin dimethylnitrosamine (24-26). The pathophysiological disturbances and histologic changes that develop over a 6-8 week period are similar in nature to those seen in Laennec's cirrhosis. In this model, sodium retention and increases in plasma volume precede formation of ascites by about 10 days (24). In order to exclude the possibility that the increase in plasma volume was solely due to an increased splanchnic plasma volume, repeat measurements were obtained after ligation of the superior and inferior mesenteric arteries, the celiac axis, and portal vein. In this way any contribution of the

splanchnic circulation could be excluded. These studies clearly showed that extrasplanchnic plasma volume was elevated at a time when dogs were in positive sodium balance. To further prove that extrasplanchnic plasma volume was increased, end-to-side portacaval shunts were placed prior to inducing cirrhosis (26). This maneuver was designed to prevent any increase in splanchnic plasma volume. In these studies, evidence of salt retention preceded the formation of ascites and was accompanied by a parallel increase in plasma volume.

In another series of studies using this same model, hemodynamic parameters were monitored during control, precirrhotic, and postcirrhotic sodium balance periods (25). Sodium retention was found to precede any detectable change in cardiac output or peripheral vascular resistance. Once ascites developed, plasma volume increased further and this was associated with increased cardiac output and a fall in peripheral vascular resistance. It was concluded that initiation of sodium retention and plasma volume expansion was not dependent on alterations in systemic hemodynamics. This conclusion has been corroborated in the canine model of hepatic cirrhosis induced by bile duct ligation (27) as well as in rats made cirrhotic with carbon tetrachloride inhalation and oral phenobarbital (28).

The pathway by which primary renal sodium retention would be linked to venous outflow obstruction in the overfill hypothesis is not clear. Convincing evidence does exist for the presence of an intrahepatic sensory network composed of osmoreceptors, ionic receptors, and baroreceptors (29). Studies in which hepatic venous pressure is raised have demonstrated increases in hepatic afferent nerve activity (27,29,30-32). Furthermore, a neural reflex pathway linking hepatic venous congestion and augmented sympathetic nerve activity has been identified (33). In addition, acute constriction of the portal vein in dogs results in renal sodium and water retention in the innervated unilateral kidney, while these effects are abolished in the contralateral denervated kidney (34). In addition to a neural mechanism there may also be a hormonal system by which the liver and kidney can communicate. Bankir et al., has recently suggested that hepatically produced cAMP may be one such hormone (35). Circulating cAMP is known to inhibit proximal salt and water absorption as well as contribute to the regulation of glomerular filtration rate. According to this hypothesis decreased circulating cAMP levels as a result of liver disease could secondarily lead to renal salt retention and impaired renal function.

In summary, the overfill hypothesis is supported by a number of observations that indicate sodium retention precedes development of ascites in the absence of hemodynamic factors known to lead to salt retention. Moreover, high cardiac output coupled with increased plasma volume argue strongly for increased arterial blood volume, a finding seemingly incompatible with the underfill theory. Against such an analysis, however, is that mechanisms that sense arterial volume physiologically may be more sensitive than methods used to measure it. It should be noted that while statistically insignificant there was a fall in blood pressure at the time of positive sodium balance in the dimethylnitrosamine model. This decrease may have been of sufficient magnitude to signal renal salt retention (25). Since cardiac output was unchanged, total peripheral resistance may have decreased. Similarly, patients with hepatic cirrhosis and ascites behave as if they are effectively volume depleted. Despite an increase in cardiac output and plasma volume arterial pressure is typically low. This fall in systemic blood pressure is consistent with an underfilled arterial vascular compartment. Thus the distinction between classical and overflow theories better rests on the measurement of effective arterial blood volume (EABV).

IV. Use of EABV to Distinguish Underfill and Overfill Mechansims of Renal Salt Retention

The classical (underfill) theory predicts that EABV is low in patients with ascites and is the afferent mechanism signaling renal salt retention. The overflow theory predicts an increased EABV due to primary salt retention. While EABV cannot be measured directly, assessing the level of activation of neurohumoral effectors known to be regulated by EABV can be considered a measure of it. In this regard, levels of renin, aldosterone, antidiuretic hormone, and norepinephrine can serve as markers reflective of the magnitude of the EABV.

When renin and aldosterone values have been measured in patients with cirrhosis, values have varied from low to high. It is important, however, to consider these levels in the context of whether ascites is present or not. In the absence of ascites, subjects are in sodium balance and renin and aldosterone levels are normal (36,37). In the presence of ascites, mean renin and aldosterone levels are elevated, but individual values are often still normal (17,38,39). This observation seems in conflict with the classical theory as all patients with ascites who are in positive sodium balance should have decreased EABV and high aldosterone levels. However, not all patients with ascites are retaining sodium. In fact, some patients are in balance such that sodium intake equals output. Thus, in examining the mechanism of sodium retention in cirrhosis with ascites, renin and aldosterone levels should be considered with respect to the rate of sodium excretion (40).

When examined in this fashion, a significant inverse relationship is found between urinary sodium excretion and plasma aldosterone (17,38,39,41). In subjects with ascites who excrete 50-100 mEq of sodium per day, plasma aldosterone concentration is normal (38). As predicted by the classical theory, these patients have normal EABV and thus normal plasma aldosterone concentration. In patients with low rates of urinary sodium excretion, increased plasma aldosterone concentrations are reflective of a contracted EABV. Since aldosterone metabolism is impaired in liver disease, increased plasma concentrations could result from decreased hepatic clearance. When studied, however, increased secretion rate and not impaired metabolism is found to be the major cause of elevated aldosterone levels (42).

Measurement of plasma catecholamines to assess the level of activity of the sympathetic nervous system has been performed in subjects with cirrhosis. Similar to aldosterone, results of these measurements have been conflicting (43,44). However, when examined as a function of urinary sodium excretion rate, plasma norepinephrine and urinary sodium excretion are found to vary inversely (45). In addition, plasma norepinephrine is positively correlated with arginine vasopressin (AVP) and plasma renin activity.

Studies have also been performed in which humoral markers reflective of EABV were examined with respect to the ability to excrete water loads (45-47). In those subjects who excreted less than 80% of a water load over a 5-hr period plasma concentrations of AVP, renin, aldosterone, and norepinephrine were higher in comparison to those who were able to excrete greater than 80% of the water load (45,46). In a similar study, cirrhotic patients unable to elaborate a positive free-water clearance after administration of a water load were also shown to have higher levels of AVP, norepinephrine, and plasma renin activity (47). Furthermore, the impairment in water excretion was found to parallel the clinical severity of disease (48). Thus in patients with a low urinary sodium concentration or an impaired ability to excrete water loads, measurement of neurohumoral markers suggests the presence of a contracted EABV.

One identifiable component of the circulation that appears to be contributing to the overall decrease in EABV is the central circulation. Indirect measurements demonstrate that central blood

volume is reduced while noncentral blood volume is expanded (49-51). In fact, the size of central and arterial blood volume is inversely correlated with sympathetic nervous system activity suggesting that unloading of central arterial baroreceptors is responsible for enhanced sympathetic activity. This conclusion is supported by studies using the technique of head-out water immersion (HWI) (52,53). In this technique subjects are seated and immersed in a water bath up to their necks. This technique results in redistribution of ECF volume from the interstitial space into the vasculature with a sustained increase in central blood volume (54). The central volume expansion is comparable to that induced by infusion of 2 liters of isotonic saline (53). Such a maneuver would be expected to raise both EABV and hepatic sinusoidal pressures. The classical theory would predict that HWI would lead to decreases in renin, aldosterone, ADH, and norepinephrine concentrations in response to expansion of EABV. Since renin levels correlate with wedged hepatic vein pressures (41), the overfill theory would predict further rises in renin and other hormonal systems consequent to initiation of a sinusoidal pressure-sensitive hepatorenal reflex. When HWI was performed in a heterogeneous group of patients with cirrhosis, the natriuretic response was variable, but suppression of renin and aldosterone levels was uniform (55,56). In a more homogenous group of patients characterized by impaired ability to excrete water and sodium, HWI was shown consistently to suppress plasma AVP, renin, aldosterone, and norepinephrine as well as to increase sodium and water excretion (57,58).

Placement of a peritoneovenous shunt results in a natriuretic response in patients with cirrhosis. This procedure allows for a direct route for replenishing the intravascular space through mobilization of ascitic fluid. The decrease in plasma renin activity and serum aldosterone levels after peritoneovenous shunting lends further support for a contracted EABV in these patients (59). Similar benefits have been reported in cirrhotic patients treated with the transjugular intrahepatic portal-systemic shunt (20,60). Furthermore, the observation that paracentesis without intravenous albumin increases plasma renin activity and impairs renal function in most cirrhotic patients argues against the overflow theory of ascites (61). Taken together, the multiplicity of data support the presence of decreased EABV in patients with decompensated cirrhosis and is most consistent with the underfill theory. Since blockade of endogenous vasoconstrictor systems in patients with cirrhosis and ascites leads to marked arterial hypotension, activation of these systems function to contribute to the maintenance of arterial pressure. At least one component of the decrease in EABV may be due to an underfilled central circulation. As discussed in the following paragraphs, increased perfusion of arteriovenous communications, systemic vasodilation, and increased perfusion of the splanchnic bed are probably the main causes for this shift in blood volume from the central parts of the circulation.

V. Hyperdynamic Circulation in Cirrhosis

A. Arteriovenous Communications

The characteristic circulatory changes observed in both animal and clinical studies of cirrhosis consist of increased cardiac output, low mean arterial pressures, and low peripheral vascular resistance (21,22). The most attractive explanation for a contracted EABV in the setting of such a hyperdynamic circulation assigns a pivotal role to increased vascular capacitance. An increased vascular holding capacity out of proportion to plasma volume results in an underfilled circulation and decreased EABV. One factor that may account for increased vascular capacitance and a hyperdynamic circulation is the formation of widespread arteriovenous communications (62,63). In cirrhotics arteriovenous fistula formation has been identified in the pulmonary,

mesenteric, and upper and lower extremity circulations (63). In addition, increased blood flow has been measured in muscle and skin of the upper extremity not attributable to increased oxygen consumption, anemia, or thiamine deficiency (64). Postmortem injection demonstrated intense proliferation of small arteries in the splenic vasculature of patients with cirrhosis (65)

The hemodynamic changes and salt retention that occur with an arteriovenous fistula are reminiscent of what occurs in cirrhotic humans (66). With an open fistula, peripheral vascular resistance falls, cardiac output increases, and diastolic and mean blood pressures fall. The proportionately greater increase in vascular capacitance over cardiac output results in a contracted EABV. Consequent sodium retention expands ECF volume, raises venous filling pressure, and further increases cardiac output until balance is achieved between cardiac output and lowered peripheral resistance. At this point sodium intake equals excretion, EABV is normalized, and the patient is in balance.

In cirrhosis, a similar imbalance occurs between plasma volume and vascular capacitance such that EABV remains contracted and renal sodium retention is stimulated. In contrast to a simple arteriovenous fistula, however, several factors are present in cirrhosis that make sodium balance more difficult to achieve. First, these patients often have impaired cardiovascular function (62). Diminished venous return consequent to tense ascites or cardiomyopathy from alcohol or malnutrition may limit increases in cardiac output. Furthermore, depression of left ventricular function in response to increased afterload suggests subclinical cardiac disease despite elevated forward output (67). Second, retained sodium does not remain in the vascular space and lead to increased venous return. Rather, retained sodium becomes sequestered within the abdomen as ascites. Third, increased vascular permeability may further impair ability of retained sodium to expand EABV. Peripheral arterial vasodilation in cirrhotic rats is associated with increased vasopermeability to albumin, electrolytes, and water (68). Examination of interstitial fluid dynamics by means of a subcutaneous plastic capsule reveals substantial increases in interstitial fluid volume early in cirrhosis before appearance of ascites or peripheral edema (69). Such capillary leakage impedes filling of the intravascular compartment and prevents replenishment of a contracted EABV.

B. Primary Arterial Vasodilation

Arteriovenous fistulas and formation or hyperdynamic perfusion of preexisting capillary beds are changes that develop as cirrhosis progresses. Nevertheless salt retention occurs early in the cirrhotic process before these anatomic changes are fully established. Since sodium retention antedates the formation of overt ascites and portosystemic shunting, peripheral arterial vasodilation has been proposed to be a primary event in the initiation of sodium and water retention in cirrhosis (70,71). In this manner a decreased EABV and increased vascular capacitance could still be the signal for renal salt retention even in the earliest stages of liver injury. The peripheral arterial vasodilation hypothesis is supported by several studies in animal models. In rats with partial ligation of the portal vein, evidence of a reduced systemic vascular resistance precedes the onset of renal salt retention (72). In addition, a direct correlation has been found between the onset of decreased arterial pressure and renal sodium retention in the spontaneously hypertensive rats with experimental cirrhosis (28). As opposed to the classical underfilling theory, the arterial vascular underfilling would not be the result of a reduction in plasma volume, which in fact is increased, but rather to a disproportionate enlargement of the arterial tree secondary to arterial vasodilation (17). In the rat with carbon tetrachloride-induced cirrhosis, the fall in peripheral vascular resistance and hyperdynamic circulatory state precede ascites formation suggesting that generalized

vasodilation is indeed an early finding with hepatic injury (73).

Perhaps the best evidence to date in support of an underfilled circulation due to arterial vasodilation comes from human studies of HWI accompanied by infusion of a vasoconstrictor (74). During HWI alone urinary excretion rates of salt and water improve but do not normalize (57). Since systemic vascular resistance falls during HWI, it was proposed that further vasodilation may prevent complete restoration of EABV in subjects already peripherally vasodilated. In six subjects with decompensated cirrhosis, HWI or infusion of norepinephrine alone failed to significantly increase urinary sodium excretion. However, when norepinephrine was infused during HWI so as to attenuate the fall in systemic vascular resistance, sodium excretion increased significantly. The increase in urinary sodium extrapolated over a 24-hr period was greater than sodium intake (74). These results are consistant with the hypothesis that arterial vasodilation causes an abnormal distribution of the total blood volume such that effective central blood volume is reduced.

1. Splanchnic Arterial Vasodilation

As alluded to earlier arterial vasodilation is particularly marked in the splanchnic arteriolar bed (12,75,76). Increasing degrees of splanchnic vasodilation contribute to the fall in mean arterial pressure and unloading of baroreceptors in the central circulation (77). As a result, central afferent sensors signal the activation of neurohumoral effectors which in turn decrease perfusion of other organs but in particular the kidney. The importance of splanchnic vasodilation in the genesis of renal ischemia has been indirectly illustrated by the response to ornipressin, an analog of AVP that is a preferential splanchnic vasoconstrictor (78-80). The administration of ornipressin to patients with advanced cirrhosis leads to correction of many of the systemic and renal hemodynamic abnormalities that are present. These include an elevation in mean arterial pressure, reductions in plasma renin activity and norepinephrine concentration, and increases in renal blood flow, glomerular filtration rate, and urinary sodium excretion and volume.

2. Role of Nitric Oxide in Arterial Vasodilation

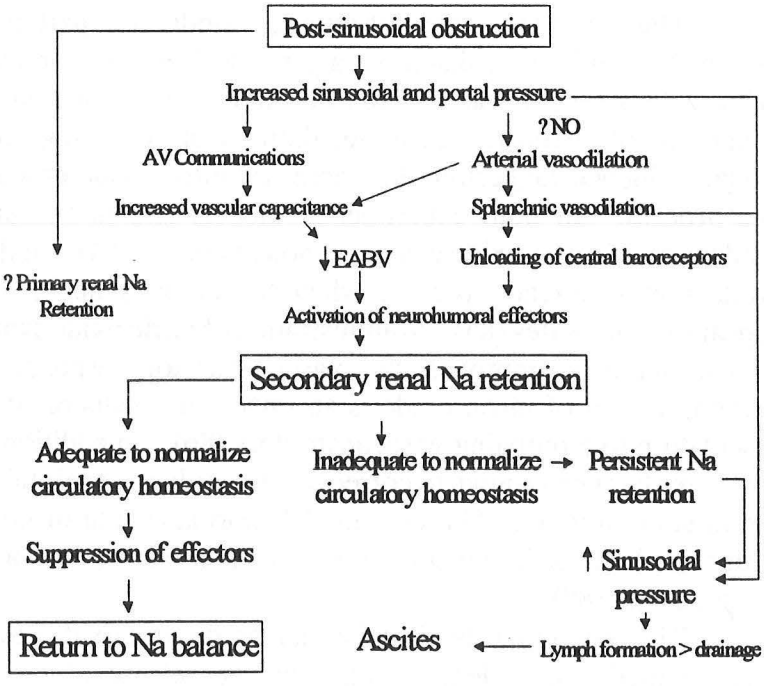
The underlying cause of arterial vasodilation particularly in the early stages of cirrhosis has not been fully elucidated but a great deal of attention has been focused on humoral factors. Table 2 lists several vasodilators that have been proposed to play a role in the hyperdynamic circulation of cirrhosis. Of these, there is an increasing body of experimental and preliminary human evidence suggesting that increased nitric oxide production may be an important factor in this process. In both experimental models and in human subjects with cirrhosis increased production of nitric oxide can be demonstrated (81-84). In the cirrhotic rat evidence of increased production is already present when the animals begin to retain sodium and antedates the appearance of ascites (85). Administration of nitric oxide synthase inhibitor L-NMMA to cirrhotic human subjects improves the vasoconstrictor response to noradrenaline suggesting that overproduction of nitric oxide is an important mediator of the impaired responsiveness of the vasculature to circulating vasoconstrictors (86). In addition, this same inhibitor administered in low doses has been shown to correct the hyperdynamic circulation in cirrhotic rats (87). In a more recent study utilizing this same model, normalization of nitric oxide production was associated with a marked natriuretic and diuretic response as well as a reduction in the degree of ascites in cirrhotic rats (88).

The precise mechanism for increased nitric oxide production in cirrhosis is not known but may be mediated at least in part via the release of tumor necrosis factor-alpha (89). In

experimental models of hepatic disease, for example, the administration of anti-TNF-alpha antibodies or an inhibitor of nitric oxide synthesis results in increases in splanchnic and total vascular resistance, an elevation in the mean arterial pressure, and a reduction in cardiac output toward or, with nitric oxide inhibition, to normal (87,89). Similarly, blocking the signaling events induced by TNF and nitric oxide production, via inhibition of protein tyrosine kinase, ameliorates the hyperdynamic abnormalities in rats with cirrhosis and portal hypertension (90). Studies in cirrhotic humans with an increased cardiac output and systemic vasodilatation have shown evidence of enhanced nitric oxide production, a finding compatible with the experimental observations (81).

In patients with cirrhosis, portosystemic shunts and decreased reticuloendothelial cell function allow intestinal bacteria and endotoxin to enter the systemic circulation. Increased circulating endotoxin levels could be a potential stimulus for tumor necrosis factor-alpha and/or nitric oxide production. To test this possibility, Chin-Dusting et al., examined the effect of administering a fluoroquinolone antibiotic on hemodynamics in a group of well-compensated human cirrhotic patients (91). It was postulated that the antibiotic would decrease the level of circulating endotoxin and nitric oxide and improve peripheral hemodynamics. At baseline patients with cirrhosis had increased basal forearm blood flow as compared to normal controls. Administration of the nitric oxide inhibitor, N^G-monomethyl-L-arginine decreased forearm blood flow both in normals and in cirrhotic patients but the effect was greater in patients with cirrhosis. This increased response suggested that nitric oxide was responsible for peripheral vasodilation in the cirrhotic patients. Administration of the antibiotic to cirrhotic patients was found to normalize both basal forearm blood flow as well as the response to N^G-monomethylLarginine. This study is consistent with the notion that bacterial endotoxin originating in the intestine is an important factor in stimulating nitric oxide production which in turn contributes to the arteriolar vasodilation in patients with cirrhosis.

It is not yet known with certainty whether the endothelial (eNOS) or the inducible (iNOS) isoform is primarily responsible for increased production of nitric oxide. It has been suggested that the hyperdynamic circulatory state of cirrhosis may increase shear stress and thereby provide a stimulus for the upregulation of eNOS (84,92). Increased activity of nitric oxide synthase in polymorphonuclear cells and monocytes (cells that primarily contain iNOS) described in cirrhotic huamn subjects suggest the inducible isoform may also play a role in increased production (81,92).



In summary, an underfill mechanism appears to explain the bulk of both experimental and clinical findings in established cirrhosis (Fig. 9). Less certain are mechanisms responsible for sodium

retention that precede the development of ascites. The overfill theory invokes the presence of a hepatorenal reflex sensitive to subtle rises in intrahepatic pressure mediating initiation of renal salt retention. However, the finding of decreased peripheral vascular resistance even at this early stage suggests diminished arterial filling (25). Early peripheral arterial vasodilation and later formation of anatomic shunts lead to disproportionate increases in vascular capacitance with subsequent contraction of EABV, thereby signaling renal salt retention. While it is conceivable that both overfill and underfill mechanisms may be operative at different stages of disease, the multiplicity of data both clinical and experimental can be assimilated into an underfill theory.

VI. Concept of Balance in Cirrhosis

In the earliest stages of cirrhosis when arterial vasodilation is moderate and the lymphatic system is able to return increased lymph production to the systemic circulation, renal sodium and water retention is sufficient to restore EABV and thereby suppress neurohumoral effectors. Balance is reestablished such that sodium intake equals sodium excretion but at the expense of an increased ECF volume. As the liver diseases progresses this sequence of arterial underfilling followed by renal salt retention is repeated. As long as the EABV can be restored to near normal levels the activation of effector mechanisms will be moderated and balance will be achieved albeit at ever increasing levels of ECF volume. Eventually lymph production will begin to exceed the drainage capacity of the lymphatic system. At this stage of the disease renal salt retention becomes less efficient at restoring EABV as retained fluid is sequestered in the peritoneal cavity as ascites. At the same arterial underfilling is more pronounced particularly as splanchnic arteriolar vasodilation becomes more prominent. Activation of neurohumoral effectors is magnified resulting in more intense renal salt retention. Even at this stage of the disease cirrhotic patients with ascites eventually reestablish salt balance. The terminal stages of the cirrhotic process is characterized by extreme arterial underfilling. At this time there is intense and sustained activation of neurohumoral effectors. As a result renal salt retention is nearly complete as the urine becomes virtually devoid of sodium. The vasoconstrictor input focused in on the kidney is of such a degree that renal failure begins to develop.

VII. Effector Mechanisms in Cirrhosis

A. Nephron Sites of Renal Sodium Retention

1. Glomerulus

Commonly applied clinical and laboratory criteria may not accurately assess GFR in subjects with cirrhosis (93). The serum creatinine may remain normal despite falls in GFR to less than 25 ml/min. Coexistence of cachexia and low creatinine generation rates make use of creatinine clearance an unreliable indicator of GFR (94). In fact, creatinine clearance can overestimate GFR when measured by inulin clearance by a factor of 2 in patients with cirrhosis and a normal serum creatinine (93). Nevertheless, whether GFR is diminished or supernormal (95), salt retention and impaired free-water clearance are characteristic disturbances in renal function (93,96). Evidence is available to support an important role for both proximal and distal nephron segments in mediating enhanced sodium reabsorption.

2. Proximal Nephron

Indirect evidence supporting enhanced proximal salt reabsorption comes from studies in

human cirrhotic subjects in which infusion of mannitol or saline improves free-water clearance (97,98). Increased proximal tubular salt reabsorption leads to decreased delivery of filtrate to the distal diluting segments, thereby impairing free-water formation. Presumably, by restoring distal delivery of filtrate, mannitol and saline infusions result in increased solute free-water formation. Similar increases in free-water clearance were noted in subjects in which central hypervolemia was induced by HWI (56). In this study, marked natriuresis was accompanied by increased K excretion, suggesting enhanced distal delivery of sodium. Increased water excretion seen in response to HWI combined with simultaneous infusion of norepinephrine is also consistent with baseline enhanced proximal sodium reabsorption in decompensated cirrhotics (74). Since plasma ADH fell to the same extent in both the combined maneuver and HWI alone, it was concluded that augmented water excretion during the combined maneuver was attributable to increased distal delivery. Studies using the clearance of lithium as a marker of proximal tubular sodium handling also indicate the proximal nephron as the main site responsible for tubular sodium reabsorption (99). Renal sodium handling has also been assessed in cirrhotic patients with no peripheral edema or ascites (100). Proximal fractional reabsorption of sodium was estimated using clearance techniques in the presence of a hypotonic diuresis. In these patients, proximal fractional sodium reabsorption failed to decrease in response to saline loading. Similar findings were found in studies examining the magnitude of renal sodium absorption that remained after ethacrynic acid and chlorothiazide therapy (101). Diuretic-resistant sodium reabsorption was found to be greater in cirrhotic patients as compared to normal controls, suggesting stimulated proximal salt absorption.

Experimental models of cirrhosis have provided more direct assessment of nephron function (102-104). Micropuncture studies in rats made cirrhotic by ligation of the common bile duct demonstrated increases in both proximal tubule solute reabsorption and filtration fraction (102). Enhanced proximal reabsorption was attributed to increased peritubular oncotic pressure. The importance of renal hemodynamic factors in abnormal renal handling of salt and water is further highlighted in studies of dogs made cirrhotic by a similar mechanism (104). In those animals chronically ligated, intrarenal administration of the vasodilator acetylcholine was found to ameliorate the blunted natriuretic response to saline infusion. In this model, sodium reabsorption was enhanced in both the proximal and diluting segments of the nephron (103).

3. Distal Nephron

Clinical and experimental evidence also supports an important role for distal nephron sodium retention in cirrhosis. During hypotonic saline-induced diuresis, renal sodium excretion and solute free-water clearance were measured in order to estimate distal sodium load and distal tubular sodium reabsorption (105). When compared to controls, cirrhotic patients with ascites had similar distal sodium delivery but increased distal fractional sodium reabsorption. In cirrhotic patients manifesting a sluggish natriuretic response to HWI, phosphate clearance was found similar to a group who demonstrated an appropriate increase in urinary sodium excretion (106). Since phosphate clearance was used as a marker of proximal sodium reabsorption, it was concluded that distal sodium reabsorption contributed importantly to renal sodium retention in those patients with a sluggish natriuretic response. The results of a prospective, double-blind study comparing the diuretic response of furosemide to spironolactone in cirrhotic patients with ascites suggest salt absorption in the cortical collecting tubule is enhanced (107). When administered furosemide, only 11 of 21 patients responded with a diuresis, while 18 of 19 patients responded to spironolactone. Furthermore, 10 patients who failed to respond to furosemide demonstrated a diuretic response

to spironolactone. Furosemide inhibits sodium reabsorption in the loop of Henle, thereby increasing delivery to the collecting duct. All patients treated with furosemide had increases in the rate of potassium excretion including the 11 patients who failed to increase urinary sodium excretion. These results, combined with the clinical effectiveness of spironolactone in treatment of cirrhotic ascites, suggest enhanced salt absorption in the aldosterone-sensitive cortical collecting tubule. Increased reabsorption in this segment could account for results in earlier studies which concluded that ethacrynic acid-chlorothiazide-independent sodium absorption was confined to the proximal tubule (101). Experimental models of cirrhosis also confirm an important role for distal nephron-mediated sodium reabsorption (108).

In summary, clinical and experimental studies suggest an important role for both proximal and distal nephron sites mediating renal salt retention in cirrhosis. The relative contribution of different nephron sites to impaired salt and water excretion may depend on the degree to which systemic hemodynamics are altered. With each stage of advancing liver disease there becomes a greater contraction of the EABV. In the earliest stages of liver disease enhanced proximal reabsorption limits distal delivery of solute in a manner analogous to a nonedematous subject with intravascular volume depletion. If distal delivery can be normalized at this early stage, distal nephron sites may continue to reabsorb sodium avidly and therefore appear as the primary site responsible for ECF volume expansion. With severe reductions in EABV, presumably the proximal nephron becomes the dominate site of fluid reabsorption such that the contribution of the distal nephron becomes much less apparent.

B. Sympathetic Nervous System

The sympathetic nervous system has been shown to importantly contribute to abnormalities in body fluid homeostasis in cirrhosis. Studies in rats made cirrhotic by ligating the common bile duct suggest that increased renal nerve activity is a major factor in the progressive salt retention that occurs in these animals (109,110). In this model baseline renal nerve activity is increased and fails to decrease appropriately in response to intravenous saline. Renal denervation significantly improves the impaired ability to excrete both an oral or intravenous salt load. In addition, renal denervation has been shown to normalize the attenuated diuretic and natriuretic response to the intravenous administration of atrial natriuretic peptide (111). In chronic metabolic studies, renal denervation also leads to a significant improvement in the positive cumulative sodium balance. The cause of the increased renal nerve activity is multifactorial. Recent studies have demonstrated an impairment in both aortic and cardiopulmonary baroreceptor regulation of efferent renal nerve activity (112). In dogs with chronic bile duct ligation, renal nerve activity fails to decrease in response to high NaCl food intake (113). This defect has been attributed to abnormalities in hepatic NaCl-sensitive receptors or their immediate intrahepatic afferent connections.

Studies in human cirrhotic subjects are more indirect but also suggest an important role for the sympathetic nervous system. Levels of norepinephrine in patients with cirrhosis vary from normal to elevated. When measured in decompensated cirrhosis, levels are high and are inversely correlated with urinary sodium excretion (45). Confirming that plasma norepinephrine levels are in fact an index of sympathetic activity and not simply the result of impaired clearance, measurement of hepatic extraction of norepinephrine has been found normal in decompensated cirrhosis (58,114). In addition, direct measurement of peripheral nerve firing rates show evidence of increased central sympathetic activity. Patients characterized by impaired ability to excrete water loads have plasma levels of norepinephrine which correlate positively with levels of ADH, aldosterone, and plasma renin activity (45). Decreased EABV leads to baroreceptor-mediated

activation of sympathetic nerve activity with subsequent enhancement of proximal salt reabsorption. Renal nerve-mediated decrease in sodium delivery to the diluting segment in addition to nonosmotic release of ADH contributes to the inability to maximally excrete water loads. Furthermore, increased renal nerve activity can indirectly enhance distal sodium reabsorption by stimulating renin release with subsequent formation of aldosterone. If baroreceptor-mediated increases in adrenergic activity are triggered by diminished EABV, then central blood volume expansion should reverse this sequence and lower plasma norepinephrine. In addition, decreased levels of norepinephrine should be associated with an improvement in renal salt and water excretion. In this regard, cirrhotic patients subjected to HWI demonstrate significant suppression of plasma norepinephrine levels (58). Moreover, during HWI there is a significant correlation between right atrial pressure, the decrement in plasma norepinephrine, and increase in fractional excretion of sodium (57). However, other studies have not found a clear cut association between decreased circulating catechols and an improved renal excretory response. In a study of patients with decompensated cirrhosis subjected to HWI there was a striking increase in creatinine clearance and a variable natriuresis that occurred independently of changes in plasma norepinephrine levels (115). Similarly, administration of the α_2 agonist, clonidine, inhibited renal sympathetic nerve activity and increased GFR and urine flow, but did not increase urinary sodium excretion (116). In another study of cirrhotic patients, clonidine was found to decrease the concentration of norepinephrine in the right renal vein but did not change GFR or urinary sodium excretion (117). These studies suggest that while sympathetic nerve activity is increased in cirrhosis, it is not the sole mechanism responsible for impaired salt and water excretion.

In addition to stimulating renal salt and water retention, increased sympathetic tone may also contribute to the renal vasoconstriction that characterizes the cirrhotic state (118-120). Renal nerves are also likely to be one of several factors responsible for the intense vasoconstriction that characterizes the hepatorenal syndrome (121). Activation of the sympathetic nervous system may serve as a compensatory response to cirrhosis-induced vasodilation. In cirrhotic patients, infusion of the adrenergic blocking agent phentolamine into the renal artery resulted in systemic hypotension (122). The heightened sensitivity of blood pressure to phentolamine infusion is consistent with an important role of sympathetic nerves in maintaining vascular tone.

In summary, the sympathetic nervous system is activated under conditions of decompensated cirrhosis. Overactivity of this system is the result of a contracted EABV. In addition there is impaired regulation of sympathetic outflow due to abnormalities in several afferent sensing mechanisms. Increased renal nerve activity contributes to the cumulative salt retention that accompanies advancing liver disease. In addition, activation of sympathetic outflow plays an important compensatory role in maintaining vascular tone in the setting of decreased vascular resistance.

C. Aldosterone

In patients with cirrhosis and ascites, plasma concentrations of aldosterone are frequently elevated. Although aldosterone metabolism is impaired in liver disease, secretion rates are greatly elevated and are the major cause of elevated levels (42). The relationship between hyperaldosteronism and sodium retention is not entirely clear. Several studies have provided evidence which argue against an important role of aldosterone in mediating salt retention in cirrhosis. For example, patients treated with an aldosterone synthesis inhibitor do not necessarily exhibit a natriuretic response (42). In one study, renal salt excretion and changes in plasma renin and aldosterone levels were examined in 11 patients with ascites subjected to 5 days of high-salt

intake. In those patients with normal suppression of renin and aldosterone, salt retention and weight gain occurred to the same extent as those patients who had persistent hypersecretion of renin and aldosterone (123). In addition, cirrhotic patients in positive sodium balance as compared to controls with matched sodium excretion have increased fractional distal sodium reabsorption despite lower plasma aldosterone levels (37). In 16 cirrhotic patients subjected to HWI, plasma renin activity and plasma aldosterone levels were found to decrease promptly. Despite suppression of the hormones, however, half of the patients manifested a blunted or absent natriuretic response (124). In another group of cirrhotic patients with ascites and edema, HWI induced a significant natriuresis despite acute administration of desoxycorticosterone, suggesting that enhanced sodium reabsorption can occur independently of increased mineralocorticoid activity (125).

In contrast, a number of observations support aldosterone as an important factor in the pathogenesis of sodium retention in patients with cirrhosis. For example, adrenalectomy or administration of a competitive inhibitor of aldosterone increases urinary sodium excretion (126). Patients who fail to manifest a diuretic response to furosemide tend to have higher renin and aldosterone levels and lower urinary sodium concentrations prior to treatment (103). Inability of furosemide to increase urinary sodium in these patients may result from reabsorption of delivered sodium in the collecting tubule under the influence of aldosterone. Similarly, patients with the highest renin and aldosterone levels are those who fail to diurese in response to HWI (48,124). In order to more clearly define the relationship between sodium excretion and plasma aldosterone levels, patients with decompensated cirrhosis were subjected to HWI in combination with infused norepinephrine (127). It was hypothesized that in the setting of decreased EABV, inability to escape from the sodium-retaining effects of aldosterone results from enhanced proximal sodium reabsorption and therefore decreased distal sodium delivery. Use of HWI combined with norepinephrine so as to maintain peripheral vascular resistance provides the most effective means of increasing central blood volume and restoring EABV (74). In this study, the combined maneuver resulted in the largest negative sodium balance and suppressed plasma renin activity and aldosterone levels to a greater extent than HWI or norepinephrine alone.

As with the conflicting data regarding the role of the proximal and distal nephron in salt retention discussed previously, the degree to which systemic hemodynamics and EABV are impaired may explain some of the conflicting data noted above. It is possible that in those patients with the greatest contraction of EABV intense proximal sodium reabsorption limits distal delivery to such an extent that the contribution of aldosterone to increase salt absorption is difficult to detect. By contrast, with less impairment of the EABV, distal delivery is better maintained such that the aldosterone-mediated sodium reabsorption becomes more obvious. In this regard, aldosterone has been shown to contribute to the exaggerated salt retention that occurs in the upright position in patients with early cirrhosis without ascites (128).

D. Prostaglandins

The observation that nonsteroidal anti-inflammatory drugs decrease GFR, renal blood flow, and sodium excretion suggests that prostaglandins may serve a protective role in cirrhosis. Ligation of the common bile duct in dogs results in enhanced synthesis of vasodilatory prostaglandins. When inhibited with indomethacin, renal blood flow and GFR are reduced significantly (129). A similar protective effect may be present in cirrhotic humans (130,131). Administration of indomethacin to patients with alcoholic liver disease results in both reduced effective renal plasma flow and creatinine clearance. These parameters were corrected when

prostaglandin E_1 was infused intravenously (131).

Prostaglandins may also importantly influence renal salt and water handling in cirrhosis. Patients pretreated with indomethacin exhibit a blunted natriuretic response to diuretics known to increase renal prostaglandin synthesis (132). In comparison to normal controls, patients with decompensated cirrhosis subjected to HWI demonstrate a threefold greater increase in PGE excretion, which is accompanied by increased creatinine clearance and sodium excretion (133). In subjects with ascites, impaired ability to clear free water is associated with lower urinary PGE_2 (47). Intravenous infusion of lysine acetylsalicylate reduced the clearance of free water, while GFR was variably affected. Diminished synthesis of prostaglandins may leave vasopressin-stimulated water reabsorption unopposed, thereby reducing free-water clearance. Prostaglandins may also participate in blood pressure homeostasis. In cirrhotic patients the pressor response to infused AII is impaired (134). Administration of either indomethacin or ibuprofen results in significant decreases in renin and aldosterone levels and restores pressor sensitivity to infused AII (135).

In summary, prostaglandins function in a protective role in decompensated cirrhosis. Similar to other hypovolemic states, prostaglandins act to maintain renal blood flow and GFR by ameliorating pressor effects of AII and sympathetic nerves (136). These agents may also serve to mitigate the impairment in free-water clearance that would otherwise occur from unopposed activity of AVP. Administration of prostaglandin inhibitors can partially correct excessive hyperreninemia and hyperaldosteronism and restore the pressor response to AII.

E. Kallikrein-Kinin System

Urinary kallikrein activity is increased in cirrhotic patients with ascites and preserved GFR while urinary activity decreases in association with impaired renal function (137). The correlation between renal plasma flow and GFR suggests the renal kallikrein-kinin system may contribute to maintenance of renal hemodynamics in cirrhosis.

At the level of the renal tubule bradykinin has been shown to exhibit a natriuretic effect. However, bradykinin also is a potent peripheral vasodilator and can cause microvascular leakage. In cirrhosis, these later effects could exacerbate an already contracted EABV and cause further salt retention. MacGilchrist et al., studied the effects of kinin inhibition by systemically infusing aprotinin (a strong inhibitor of tissue kallikrein) into a group of patients with cirrhosis (138). This infusion was associated with a doubling of urinary sodium excretion and an increase in renal plasma flow and GFR. This beneficial effect on renal function in the setting of kinin inhibition was attributed to an improvement in systemic hemodynamics as systemic vascular resistance increased. Similarly, administration of a bradykinin β_2 receptor antagonist to cirrhotic rats normalized renal sodium retention and reduced the activity of the renin-angiotensin-aldosterone system (139). Inhibiting bradykinin-induced microvascular leakage and lessening the degree of vascular underfilling was felt to be the mechanism of the beneficial effect.

F. Natriuretic Peptides

The role of ANP in the pathogenesis of edema in hepatic cirrhosis remains undefined. While atrial ANP content was reduced in cirrhotic rats, most data indicate ANP levels are either normal or elevated in cirrhotic humans (140,141). Elevated levels are the result of increase cardiac release rather than just impaired clearance. The cause of the high levels is not understood, because atrial pressure is normal and central blood volume is reduced. The coexistence of normal or increased ANP levels and sodium retention suggests some degree of renal refractoriness to the

hormone. Stimulating the endogenous release of ANP induces a natriuretic response in some patients with cirrhosis while other patients are insensitive (142). However, both groups of patients exhibit an increase in urinary cGMP suggesting that the kidney is still capable of responding to ANP even in the absence of a natriuretic effect (142).

Several potential mechanisms may account for ANP resistance in cirrhosis. This resistance could be the result of a defect intrinsic to the kidney or could be the result of altered systemic hemodynamics leading to activation of more potent sodium-retaining mechanisms (140,143). With regards to the first possibility an altered density of glomerular ANP binding sites has been demonstrated in the bile duct-ligated rat model of cirrhosis (144). In addition, ANP resistance was found in the isolated perfused kidney taken from sodium avid rats with cirrhosis induced by carbon tetrachloride (145). This preparation allows systemic and hormonal factors to be excluded. In the chronic caval dog model of cirrhosis intrarenal infusion of bradykinin restored ANP responsiveness to previously resistant animals suggesting that an intrarenal deficiency of kinins could be a contributing factor (146).

Other studies have focused on systemic hemodynamics as a cause of ANP resistance. With each stage of advancing liver disease there becomes a greater reduction in EABV. Since ANP resistance tends to occur with more severe and advanced disease it is possible that ANP resistance is directly related to the impairment in EABV. Decreased EABV is associated with enhanced proximal reabsorption of solute. As a result, ANP resistance may be due to decreased delivery of salt to the site where ANP exerts its natriuretic effect. In support of this possibility ANP resistance could be restored in cirrhotic rats by infusions of vasopressors so as to normalize arterial pressure and presumably improve the decrease in EABV (147). In human cirrhotics ANP responsiveness can be markedly improved when distal sodium delivery is increased by administration of mannitol (148).

Circulating brain natriuretic peptide (BNP) levels are also increased in patients with cirrhosis (149). Infusion of BNP at a dose that elicits an increase in GFR, renal plasma flow, and urinary sodium excretion in normal controls has no effect in cirrhotic humans. The infusion is associated with an increase in urinary cGMP as well as a fall in plasma aldosterone levels suggesting that the peptide is capable of interacting with its receptor in these patients. As with ANP, the lack of natriuretic response to BNP may be due to overactivity of other antinatriuretic factors as well as decreased delivery of sodium to its tubular site of action.

Adrenomedullin is a peptide with vasodilatory properties that is highly expressed in cardiovascular tissues. Increased circulating levels that correlate with severity of disease have been described in patients with cirrhosis (150). Urodilatin is a natriuretic factor that is exclusively synthesized within the kidney. Unlike other natriuretic factors, levels are not increasd in patients with cirrhosis (151).

G. Endothelin

Increased circulating levels of endothelin have been reported in cirrhosis (152). The stimulus and pathophysiologic significance of these levels is not known with certainty. The peptide may play a role in the renal vasoconstriction seen in the hepatorenal syndrome (17, 152).

VIII. Therapeutic Implications for the Treatment of Salt Retention In Cirrhosis

Renal salt retention is the most common abnormality of renal function in chronic liver disease. Whenever urinary sodium excretion falls to an amount less than dietary salt intake ECF

volume will begin to expand and eventually lead to the development of ascites and peripheral edema. The approach to the treatment of the cirrhotic patient with ascites is to alter sodium balance in such a way that urinary sodium excretion exceeds dietary salt intake. In this manner ECF volume will contract. The ultimate goal is to reestablish salt balance at an ECF volume that is clinically associated with the absence of ascites and peripheral edema.

A. Dietary Sodium Restriction

The initial step in achieving this goal is to restrict dietary sodium intake. A reasonable starting point is a 88 mEq (2 gm) sodium diet (153). Such a regimen can lead to negative salt balance in those patients with high levels of baseline urinary sodium excretion (at least >90-100 mEq/d). In such patients salt restriction alone may lead to resolution of ascites. Additional benefit may be obtained by limiting the physical activity of cirrhotic patient. Assuming the supine posture, for example, can produce a 40% rise in creatinine clearance and up to a two fold increase in sodium excretion in comparison to the upright position (154). Even in the preascitic stage of disease subjects show an exaggerated natriuresis during bed rest as compared to healthy subjects (128,155). This natriuretic response may be due to a shift in blood volume from the splanchnic circulation to the central circulation as the patients lies down. A recent study demonstrated that moderate exercise was associated with a deleterious hemodynamic effect in a subset of nonazotemic cirrhotic patients with ascites (156). These patients were characterized by having increased plasma renin activity and norepinephrine concentration at baseline and following exercise. Following 30 minutes of moderate cycloergometric exercise, this group of patients demonstrated a 33% reduction in glomerular filtration rate and a marked impairment in free water clearance and sodium excretion.

B. Diuretic Therapy

In patients with a low level of baseline urinary sodium excretion, dietary salt restriction alone is usually not sufficient to induce negative salt balance. In this situation diuretic therapy is indicated. Spironolactone is the most commonly used first line agent for several reasons. First, while normally considered a weak diuretic, spironolactone is oftentimes found to be more clinically effective that loop diuretics in some patients with advanced disease (107). Under normal circumstances, loop and thiazide diuretics are secreted into the proximal tubular lumen where they travel down stream and exert their natriuretic effect. In the setting of cirrhosis decreased renal blood flow can limit delivery of these agents to the site of secretion in the proximal nephron. In addition, accumulation of compounds such as bile salts may compete or directly impair the secretory process. The net effect is that there is less delivery of the diuretic to its site of action and the natriuretic effect is limited (157). By contrast, spironolactone does not require tubular secretion. Rather, this agent enters the cells of the collecting tubule from the blood side. As a result, the efficacy of spironolactone is not impaired with cirrhosis. Second, spironolactone is a potassium sparing diuretic and therefore unlike loop or thiazide diuretics does not cause hypokalemia. The avoidance of hypokalemia is important in the management of cirrhotic patients as potassium depletion can contribute to the development of hepatic encephalopathy. Hypokalemia can lead to increased blood ammonia levels as a result of a stimulatory effect on renal ammonia synthesis as well as increased gastrointestinal absorption of nitrogen secondary to decreased bowel motility. In addition, as potassium exits the cell in an attempt to replete extracellular stores hydrogen ions enter the cell resulting in intracellular acidosis. The drop in intracellular pH has the effect of trapping ammonia as ammonium within the intracellular space. To the extent that

this process occurs within the central nervous system, hepatic encephalopathy becomes more likely. The initial starting dose of spironolactone is 50 mg per day but can be increased to as much as 400 mg per day, although doses higher than 200 mg per day are often poorly tolerated (158).

In those patients who fail to develop a significant diuretic response to spironolactone alone, a thiazide diuretic can be added, the dose being determined by the level of renal function. The initial dose is typically 25-50 mg per day but doses as high as 100-200 mg per day can be tried when the glomerular filtration rate is less than 20 ml/min (158). If diuresis is still inadequate, a loop diuretic such as furosemide can be given in combination with the thiazide and spironolactone. The oral dose of furosemide is usually started at 40 mg/d and can be increased to a maximum of 240 mg/d.

By reducing the amount of ascites, diuretics provide both a cosmetic and comfort benefit for the cirrhotic patient. Use of these agents has also been associated with a modest reduction in portal pressure presumably by reducing plasma volume (159).

When attempting to initiate a diuresis one must be cautious in avoiding excessive volume removal. The rate at which fluid can safely be removed in cirrhosis is dependent upon the presence or absence of peripheral edema. When a diuresis is induced, the fluid is initially lost from the vascular space; the ensuing fall in intravascular pressure then allows the edema fluid to be mobilized to replete the plasma volume. Edema mobilization is relatively rate-unlimited in patients with peripheral edema (160). In comparison, patients who only have ascites can mobilize edema fluid solely via the peritoneal capillaries. The maximum rate at which this can occur is only 300 to 500 mL/day; more rapid fluid removal can lead to plasma volume depletion and azotemia.

C. Diuretic Resistant Patients

1. Large Volume Paracentesis

Patients who fail to respond to a combination of dietary salt restriction and diuretic therapy are said to be diuretic resistant. These patients are in a state of persistent positive sodium balance and require a more invasive intervention in order to effect negative salt balance. Large volume paracentesis is a procedure in which negative salt balance is established acutely by removing some or the entire volume of ascitic fluid. In patients with virtually no sodium in the urine and who are consuming 88mEq of sodium per day, tense ascites can be avoided in most patients by removing approximately 8 liters of fluid every two weeks (161,162). With some urinary sodium present the time interval required for repeat paracentesis can be extended while excessive dietary sodium intake will tend to shorten the time interval between procedures.

Large volume paracentesis has been proven to be a safe and effective means to manage cirrhotic patients with tense ascites. In addition to cosmetic and symptomatic benefits, removal of ascites lowers intraabdominal pressure (163). Intrathoracic pressure also falls as a result of increased mobility of the diaphragm. These changes are associated with a reduction in portal pressure, increased cardiac output, decreased activation of neurohumoral effector mechanisms, and a slight improvement in the serum creatinine concentration (163,164). These effects are transient in nature returning to baseline values by six days. Large volume paracentesis has also been shown to reduce intravariceal pressure and variceal wall tension (165).

The need to administer albumin in conjunction with large volume paracentesis is controversial (166-170). The rational for administering albumin would be to minimize effective intravascular volume depletion and renal impairment that could potentially develop as ascitic fluid reaccumulates. Gines et al., studied 105 patients with tense ascites undergoing LVP and

randomized the subjects to receive albumin (10 g/L of ascites removed) or no albumin (166). Patients not receiving albumin were more likely to show signs of hemodynamic deterioration including an increase in the plasma renin activity; these patients were also much more likely to develop worsening renal function and/or severe hyponatremia (166). More recently Gines et al., performed total paracentesis in 280 patients with tense ascites and randomized the subjects to replacement with different types of colloid to include albumin, dextran 70, or polygeline (167). Postparacentesis circulatory dysfunction (defined as a >50% increase in plasma renin activity 6 days after the procedure) developed in 85 patients. Of the various replacement fluids, postparacentesis circulatory dysfunction was much less common with albumin administration (19 versus 34 and 38 percent, respectively). This benefit was limited to patients in whom at least five liters of ascitic fluid was removed.

Other studies have shown that large volume paracentesis can be performed without a deleterious effect on systemic or renal hemodynamics even though albumin has not been given (169,170). In addition there is no direct evidence that such replacement therapy impacts on the long term morbidity and mortality of patients with cirrhosis and ascites (161,162). It has been suggested that patients with advanced cirrhosis who are truly diuretic resistant may tolerate large volume paracentesis without albumin better that those patients with less severe disease. This difference may be explained by increased circulatory hyporeactivity in patients with advanced liver disease as compared to patients with less advanced disease who may be more sensitive to changes in intravascular volume (171). In considering the cost and increased logistical demands of administration, albumin does not need to be given to all patients undergoing large volume or total paracentesis. Further studies are needed to identify those individuals who would benefit most from albumin infusion.

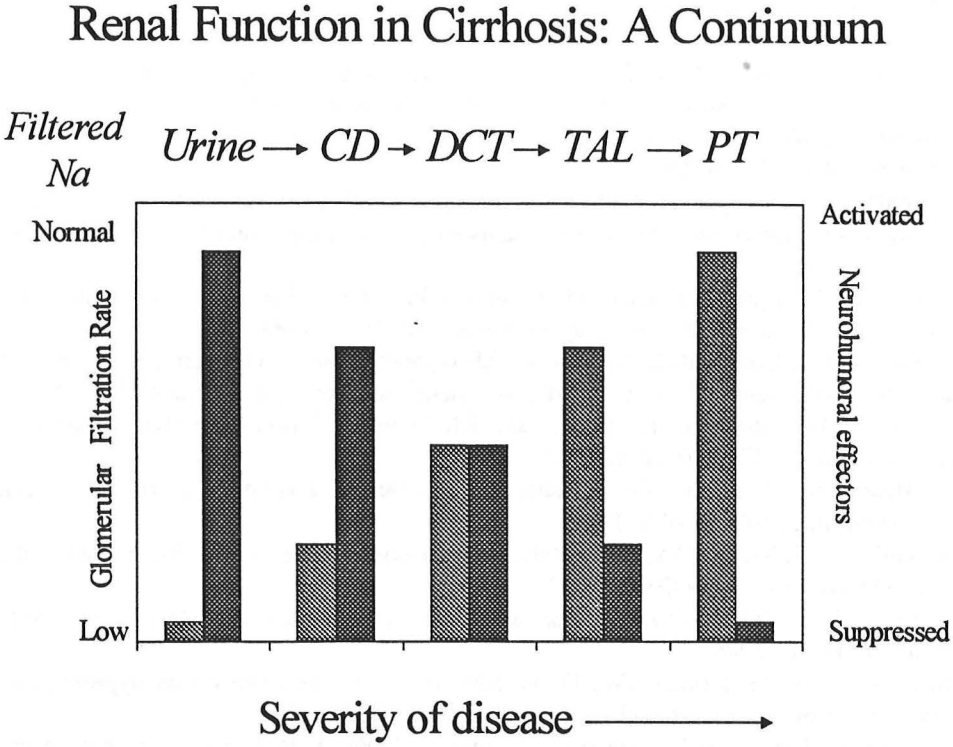
2. Peritoneovenous Shunting

Peritoneovenous shunting has been used in the treatment of diuretic resistant ascites. This procedure allows for ascites to be reinfused into the vascular space by way of the internal jugular vein. In patients with refractory ascites and renal failure due to the hepatorenal syndrome, peritoneovenous shunting has been associated with increased urinary sodium excretion and improved renal function (172,173). However the procedure is now rarely performed due to a high complication rate and the lack of survival advantage when compared to medical therapy (174,175).

3. Transjugular Intrahepatic Portosystemic Shunt

Placement of a transjugular intrahepatic portosystemic shunt (TIPS) is a procedure that lowers intrahepatic and portal pressure. TIPS has primarily been employed as a treatment to control variceal bleeding but also appears to be an effective therapy in refractory ascites. In uncontrolled studies TIPS has been shown to exert a diuretic effect sufficient enough to reduce and in some cases eliminate the presence of ascites (20,176). In those patients who respond, the dose of diuretics subsequently needed to control ascites can be markedly reduced (20,176). The maximal benefit on renal function and urinary sodium excretion is often not seen for several weeks following the procedure (177). This delayed natriuretic effect may be related to the increased systemic vasodilation that typically develops immediately after insertion of the shunt (177,178). This vasodilatory response may be due to increased delivery of vasodilators such as nitric oxide from the splanchnic circulation to the systemic circulation (178). In a small series of patients with hepatorenal syndrome, TIPS was found to improve renal function and reduce the activity of several vasocontrictor systems (179). Despite the apparent benefit, a recently published

randomized controlled trial comparing TIPS to paracentesis found that patient mortality was higher in the TIPS group, particularly in patients with Child-Pugh class C (180). In addition, TIPS placement is associated with a variety of complications to include encephalopathy and stent thrombosis or stenosis (181).



IX. Summary

The sequence in which the various therapies discussed above are instituted can be viewed as a continuum that parallels the severity of the underlying cirrhotic state. In the earliest stages of the disease urinary sodium excretion is plentiful and negative salt balance can be achieved by simply lowering dietary sodium intake. As the disease advances neurohumoral effectors become more activated initially resulting in more intense renal salt retention and later in a progressive decline in renal function. Eventually the filtered load of sodium becomes completely reabsorbed by the tubule such that the final urine becomes virtually devoid of salt. If some component of the filtered load reaches the collecting duct or beyond, spironolactone will be effective in increasing urinary sodium excretion. Once sodium reabsorption is complete proximal to the collecting duct then thiazides and later loop diuretics will have to be added to spironolactone in order to increase urinary sodium excretion. Eventually the filtered load is completely reabsorbed proximal to the thick ascending loop of Henle. At this point the patient is resistant to the effects of diuretics and requires more invasive procedures such as repetitive large volume paracentesis in order to remain in salt balance. In the terminal stages of the disease the glomerular filtration rate falls to such a degree that oliguria, azotemia, and eventually uremia are present and the patient is clinically diagnosed with hepatorenal syndrome. Vasoconstrictive input focused on the kidney is severe and irreversible. The renal failure is functional in nature, however, since restoration of near normal renal function can be obtained following a liver transplant.

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TREATMENT SUCCESS!!