An Odyssey into the Milieu Intérieur: Pondering the Enigmas[1]

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Claude Bernard, the renowned French physiologist, wrote in the 19th century, "The constancy of the milieu intérieur is the condition of free and independent existence" (1). Yet, the efforts to understand the mechanisms that underlie the maintenance of the milieu intérieur have raised several enigmas, which have led to paradoxical pathophysiological proposals. In the past, the edema in the patient with decompensated cardiac failure has been proposed to be associated with diminished plasma volume, i.e., the backward heart failure theory (2), or expanded plasma volume, i.e., the forward heart failure theory (3). These different proposals led to divergent therapeutic strategies depending on whether plasma volume was considered to be diminished or expanded, namely albumin administration or venesection, respectively. In 1952, John Peters wrote "If blood volume is necessarily increased in congestive failure, which in my opinion is not incontrovertibly established although it cannot be categorically denied, the problem remains why this disturbance, which ordinarily promotes excretion of salt, should, in heart failure, accelerate its reabsorption" (4). With the accurate methods of measuring blood volume now available, the dilemma can be even more clearly stated. Cardiac failure patients have been found to have increased blood volumes (5); thus, it is teleologically difficult to explain the continued avid sodium and water retention by the kidneys, which may lead to debilitating pulmonary congestion and peripheral edema. Moreover, it is clear that the kidneys are responding to extrarenal influences, because there is

no evidence of intrinsic renal abnormalities. A similar paradox is present in cirrhotic patients who have also been demonstrated to have increased blood volumes (6) and yet who exhibit persistent renal sodium and water retention with ascites formation and peripheral edema.

Although the methodology to measure the volumes of separate body fluid compartments including total body water, extracellular fluid volume, plasma volume, and blood volume are now available, there remains difficulty in estimating the fluid volume in the arterial circulation. Moreover, because venous blood volume has been estimated normally to constitute 85% of total blood volume, it is theoretically possible for total blood volume to be expanded secondary to increased venous volume, even though arterial blood volume is decreased. The volume of fluid in the arterial circulation not only cannot be measured accurately, but in general, the compensatory responses to arterial circulatory underfilling are so rapid and effective that the arterial pressure in any particular patient is a poor index of arterial circulating integrity. Borst and deVries suggested that a diminished cardiac output might provide the arterial signal for renal sodium and water retention in edematous disorders (7). However, it has become clear that there are states of sodium and water retention in which cardiac output is actually increased, including high-output cardiac failure, cirrhosis, sepsis, pregnancy, and agents that cause arterial vasodilation, e.g., hydralazine, minoxidil.

BODY FLUID VOLUME REGULATORY HYPOTHESIS

On this background, a body fluid volume regulatory hypothesis has emerged (8–11), which, depending on the clinical circumstance, focuses on either cardiac output or peripheral arterial vascular resistance as the primary determinants of arterial circulatory integrity. Thus, a decrease in either cardiac output (Figure 1) or peripheral arterial vasodilation (Figure 2) may initiate renal sodium and water retention by normal kidney as an integral part of the compensatory response to arterial circulatory underfilling. It is worth emphasizing that, even if available, absolute
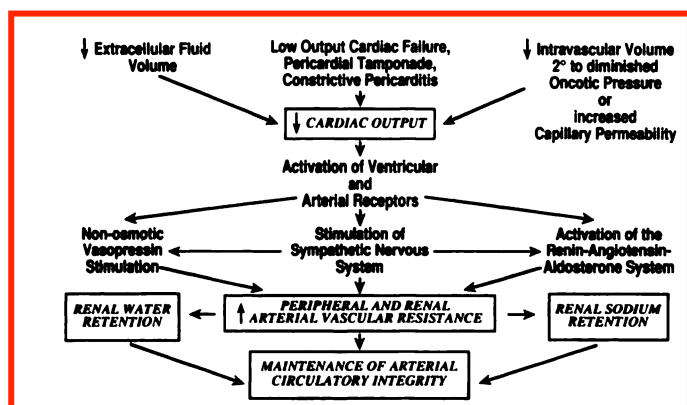
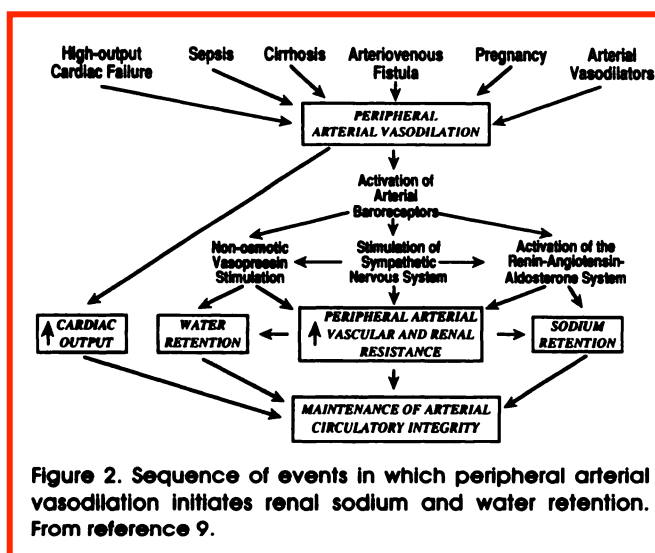Figure 1. Sequence of events in which a decrease in cardiac output initiates renal sodium and water retention. From reference 9.

Figure 2. Sequence of events in which peripheral arterial vasodilation initiates renal sodium and water retention. From reference 9.

	CLASS II	CLASS III	CLASS IV
Cardiac Index	↓	↓↓	↓↓↓
Plasma Hormones (AVP, Renin, Aldosterone, NE)	Normal	↑	↑↑
Plasma Volume	↑	↑↑	↑↑↑

Figure 3. Neurohumoral and plasma volume responses to progressive cardiac failure. New York Heart Classification II, III, and IV. NE, norepinephrine.

measurements of arterial blood volume are insufficient to assess arterial circulatory integrity. Specifically, arterial circulatory underfilling can occur with systemic arterial vasodilation when the arterial blood volume is increased in absolute terms but is relatively less than the enlarged arterial vascular holding capacity.

In the context of this volume regulatory hypothesis, a central role emerges for the sympathetic nervous system in the renal and peripheral vasoconstriction as well as activation of the renin-angiotensin-aldosterone system and the nonosmotic release of arginine vasopressin (AVP), which are observed in edematous disorders such as cardiac failure and liver cirrhosis.

CARDIAC FAILURE

Figure 3 presents a schema whereby the stages of cardiac failure are associated with progressive decreases in cardiac index, i.e., arterial underfilling, in the presence of progressive expansion of the plasma volume. In addition to the renal sodium and water

retention, neurohumoral reflexes are also progressively stimulated to compensate for arterial circulatory underfilling. In this schema, it is understandable why cardiac patients with pretreatment hyponatremia (12) and the highest plasma renin (13) and norepinephrine concentrations (14) have the worst prognosis, because they would be expected to have the lowest cardiac indices.

The role of AVP in the water retention associated with cardiac failure has been shown by (1) RIA measurements demonstrating increased AVP concentration in hyponatremic cardiac failure patients whose lowered plasma osmolality would otherwise be expected to suppress maximally plasma AVP release (15), (2) increased AVP preprohormone gene expression in the hypothalamus of rats with experimental cardiac failure (16), and (3) increased water excretion in rats with diminished cardiac output as compared with that in normal controls after the administration of a V_2 (antidiuretic) receptor AVP antagonist (17). The role of the V_1 (vascular, hepatic, and platelet) receptor in advanced cardiac failure has also been demonstrated by (1) increased platelet AVP concentrations (18), (2) down-regulation of platelet AVP receptors (19), and (3) improved cardiac output in advanced experimental (20) and human (21) cardiac failure with the administration of a V_1 antagonist.

A study by Bichet et al. (18) compared cardiac failure patients with and without detectable plasma AVP concentrations. Those patients with detectable plasma AVP concentrations demonstrated lower cardiac indices, greater impairment of water excretion, and hyponatremia, as well as higher plasma renin and aldosterone concentrations. In these heart failure patients, cardiac afterload reductions with small doses of either captopril or hydralazine increased cardiac index, improved water excretion, and suppressed plasma and platelet AVP concentrations. Taken together, these results support a diminished cardiac output as the mediator of arterial underfilling in low-output cardiac failure with resultant nonos-

motic AVP release, water retention, and hyponatremia.

The role of aldosterone in the sodium retention associated with cardiac failure has been questioned because (1) normal subjects "escape" from the sodium-retaining effects of aldosterone before the occurrence of either peripheral edema or pulmonary congestion (22) and (2) some cardiac failure patients have been shown to retain sodium in the presence of normal plasma aldosterone concentrations (23). However, with respect to the failure of "aldosterone escape" to occur in cardiac failure patients, the normal mechanisms of this phenomenon must be remembered. The normal aldosterone escape is associated with extracellular fluid volume expansion, which suppresses PRA, increases GFR, decreases proximal tubular sodium reabsorption, and thus increases sodium delivery to the distal nephron site of aldosterone action (Figure 4). In contrast, in the presence of arterial underfilling, as occurs in advanced cardiac failure and cirrhosis, there are events including a fall in GFR and increased proximal sodium reabsorption secondary to diminished renal perfusion pressure, and increased renal adrenergic and angiotensin activity, which diminishes sodium delivery to the distal nephron site of action of aldosterone (Figure 5). Thus, if increased distal sodium delivery is the primary mediator of aldosterone escape, it would be expected that states of arterial underfilling, either due to a fall in cardiac output or peripheral arterial vasodilation, would demonstrate impaired aldosterone escape (Figure 4). In this regard, renal denervation has been shown to reverse sodium retention in experimental congestive heart failure and hepatic cirrhosis (24).

With respect to sodium retention in cardiac failure patients with normal plasma aldosterone concentrations, a role of aldosterone in the sodium retention is still possible in the presence of decreased distal sodium delivery. Whereas increased distal sodium de-

Figure 4. Events involved in normal (left) and impaired (right) aldosterone escape. ECF, extracellular fluid. From reference 9.
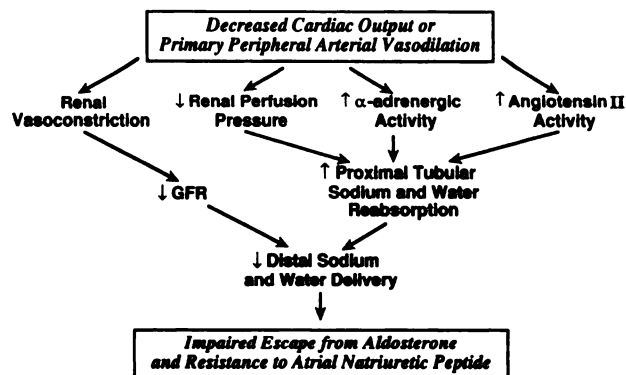

Figure 5. Mechanism whereby a decrease in cardiac output or peripheral arterial vasodilation initiates events that diminish distal sodium delivery, thereby impairing aldosterone escape and causing resistance to the natriuretic response to ANP. Adapted from reference 52.

livery may limit the sodium-retaining effect of increased aldosterone activity, i.e., aldosterone escape, it is reasonable to suggest that decreased distal sodium delivery may enhance the normal aldosterone capacity for fractional sodium reabsorption. In this regard, the administration of large doses (200 to 400 mg/day) of the competitive antagonist to the mineralocorticoid receptor, spironolactone, has been shown to increase sodium excretion in sodium-retaining cardiac failure patients with either normal or increased plasma aldosterone concentrations (25). This natriuretic response to spironolactone occurred in the presence of the simultaneous stimulation of several potential antinatriuretic factors, including increased PRA and norepinephrine concentration and decreased plasma atrial natriuretic peptide (ANP) concentration. It is thus possible that spironolactone-resistant states in cardiac failure patients may be due to insufficient doses of the antagonist or diminished distal sodium delivery secondary to the neurohumoral activation associated with arterial underfilling, an effect that can be accentuated by diuretic-induced sodium losses.

Although, as discussed, renal sodium and water excretion in cardiac failure appears to be modulated by the integrity of the arterial circulation, there is some preliminary evidence that the increase in trans-atrial pressure gradients and the resultant increased plasma ANP concentration observed with progressive cardiac failure may provide a secondary influence in modulating renal sodium excretion. This statement may seem contradictory to the observation in both human (26) and experimental (27) heart failure of a resistance to the natriuretic response to exogenous ANP. This ANP resistance, however, does not seem to be due to inactive circulating ANP, ANP receptor down-regulation, or increased renal neutral endopeptidase breakdown of ANP, because increased urinary
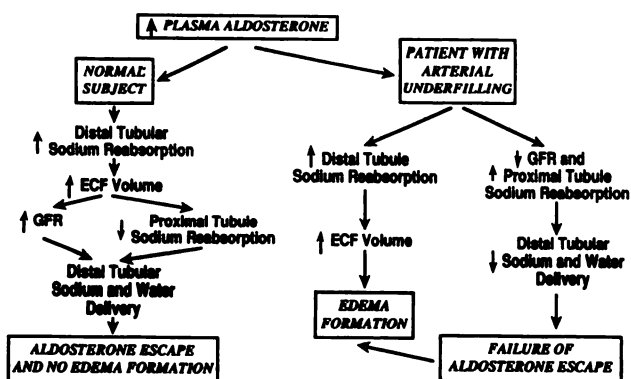
cGMP concentrations, the hormone's secondary messenger, have been shown to parallel the increased plasma ANP concentrations in heart failure patients (28). This observation has led to the proposal that, as with other hormones with distal nephron sites of action, the inner medullary collecting duct site of ANP action is also influenced by the rate of distal sodium delivery (28). Thus, diminished distal sodium delivery in heart failure may mediate not only impaired aldosterone escape but also ANP resistance (Figure 5).

Experimental evidence of a secondary modulating role of ANP on sodium excretion in heart failure, however, derives from the study of Lee and associates (29). These investigators demonstrated in dogs that for comparable decreases in mean arterial pressure, inferior vena caval constriction was more antinatriuretic than ventricular tachycardia. With ventricular tachycardia, but not caval constriction, plasma ANP concentration rose. However, when the caval dog's plasma ANP concentration was raised by infusion to a comparable level as in the ventricular tachycardia dogs, the sodium retention with caval constriction no longer occurred. Moreover, the increased plasma renin and aldosterone concentrations that occurred with caval constriction, but not with ventricular tachycardia, were returned to normal levels during the ANP infusions. These experimental results suggest that the sodium retention with cardiac failure may be delayed by the early increase in plasma ANP that occurs in heart failure, perhaps in part by suppressing the renin-angiotensin-aldosterone system. The natriuretic effect of ANP may, however, be substantially attenuated by neurohumorally mediated decreased distal sodium delivery in cardiac failure, a possibility supported by the observation that renal denervation, a maneuver known to increase distal sodium delivery, has been shown to reverse the resistance to exogenous ANP in experimental cardiac failure in rats (30).

One of the paradoxes is that sodium and water retention occurs not only with low-output cardiac failure but also with high-output cardiac failure, e.g., thyrotoxicosis, beriberi. In the context of the volume regulatory hypothesis discussed above, arterial underfilling occurs in both low-output and high-output cardiac failures, specifically, secondary to diminished cardiac output in the former and peripheral arterial vasodilation in the latter. In support of this interpretation are studies in a rat model of high-output congestive heart failure secondary to an aorta-caval fistula, which have shown that the same neurohumoral response to arterial underfilling occurs in high-output cardiac failure as reported with low-output failure (31).

In advanced cardiac failure, the compensatory responses to arterial underfilling may become maladaptive and lead to complications including pulmo-

nary congestion and myocardial ischemia (Figure 6). In the New York Heart Association Class IV heart failure patients with the highest plasma hormone concentration of catecholamines, ANP, aldosterone, and angiotensin II, the 6-month mortality has been shown to be improved with the angiotensin-converting enzyme (ACE) inhibitor, enalapril (32). Results of recent studies have suggested that ACE inhibition at earlier stages of cardiac failure may also be beneficial (33). From a pathophysiological viewpoint, however, the major therapeutic need in low-output cardiac failure is for cardiac inotropic agents, because the use of vasodilators, such as ACE inhibitors and hydralazine, is limited by the effect of these agents in larger doses to interfere with the compensatory responses to arterial underfilling and thereby to cause hypotension.

CIRRHOSIS

As with congestive heart failure, the pathophysiological debate about the sodium and water retention in cirrhosis has centered around whether blood volume is decreased or increased. The "classical underfilling hypothesis" (34) of renal sodium and water retention in cirrhosis proposed that portal hypertension leads initially to ascites formation with a resultant decrease in blood volume. The decrease in blood volume is then the proposed cause of the renal sodium and water retention. In contrast, the "overflow hypothesis" (35) suggests that cirrhosis, by an unde-
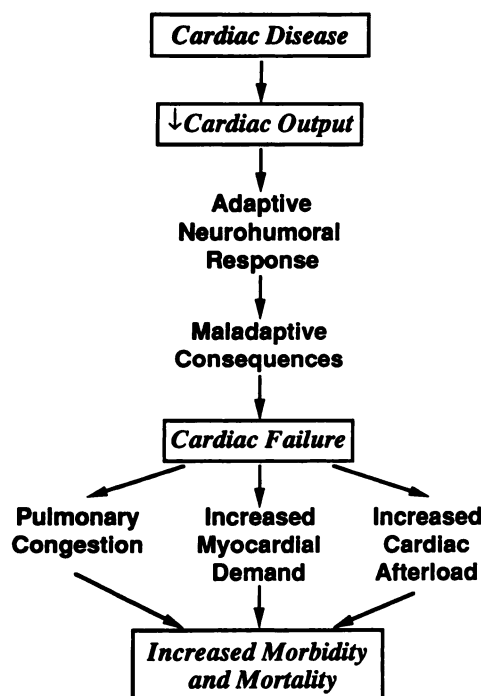

Figure 6. Compensatory responses become maladaptive in advanced cardiac failure.

termined mechanism, causes primary renal sodium and water retention independent of any volume stimulus. This renal sodium and water retention is then proposed to result in blood volume expansion. With accurate measurements of blood volume, it is not only well documented that blood volume is expanded in cirrhotic patients but also that this volume expansion precedes the occurrence of ascites (36,37). Although these findings favor the overflow hypothesis, it is clear that this latter hypothesis cannot explain the entire spectrum of cirrhosis from the compensated (no ascites) to the decompensated (ascites) state to the hepatorenal syndrome. Specifically, the progression of the stages of cirrhosis is associated with the activation of the neurohumoral profile of arterial underfilling in spite of plasma volume expansion. It is these observations that have led to the "peripheral arterial vasodilation hypothesis" (10). As shown in Figure 7, progressive arterial vasodilation is associated with the activation of the compensatory neurohumoral profile for arterial underfilling because the sodium and water retention leads to progressive plasma volume expansion (38). Thus, in spite of the plasma volume expansion, there is relative underfilling of the arterial circulation because of the vasodilation that occurs in the splanchnic, pulmonary, muscle, and dermal vascular beds. It should be clear that the peripheral arterial vasodilation hypothesis does not exclude sodium-retaining hepatorenal reflexes, such as those initiated by portal hypertension (39) or by an increase in intrahepatic pressure (40). It is known, however, that the peripheral arterial vasodilation occurs very early in the course of cirrhosis and portal hypertension (37,41). Thus, by itself, any hepatorenal reflex may not cause expansion of the arterial circulation, i.e., the overflow hypothesis. For example, in a recent study in the spontaneously hypertensive rat with experimental cirrhosis, the onset of the renal sodium retention occurred simultaneously with the decrease in arterial pressure, thus suggesting that in the rat there may not even be a

	COMPENSATED CIRRHOSIS (NO ASCITES)	DECOMPENSATED CIRRHOSIS (ASCITES)	HEPATORENAL SYNDROME
Peripheral Arterial Vasodilation	↑	↑↑	↑↑↑
Plasma Hormones (AVP, Renin, Aldosterone, NE)	Normal*	↑	↑↑
Plasma Volume	↑	↑↑**	↑↑↑**

Figure 7. Peripheral arterial vasodilation hypothesis. *Normal plasma hormone concentrations indicate relative stimulation in the presence of plasma volume expansion. **Hypoalbuminemia may attenuate plasma volume expansion. NE, norepinephrine. From reference 38.

transient phase of "overflow" with arterial overfilling (42). On the other hand, Levy and Allotey (43) observed a 20-mEq/day positive sodium balance in the cirrhotic dog 2 wk before a detectable fall in peripheral vascular resistance. The mean arterial pressures (120 and 115 mm Hg) before sodium retention were, however, higher than the mean arterial pressure (110 mm Hg) at the time of the 20-mEq/day positive sodium balance. A modest fall in peripheral vascular resistance, therefore, could have occurred and accounted for this early 20-mEq/day positive sodium balance. Thus, although hepatorenal reflexes are likely to contribute, along with peripheral arterial vasodilation, to the renal sodium and water retention associated with cirrhosis, any phase of absolute expansion of the arterial circulation, i.e., the overflow hypothesis, must be either very early and transient or nonexistent.

As with cardiac failure, after many years of conflicting results with bioassay determinations, sensitive RIA for plasma AVP have established that hyponatremic cirrhotic patients have elevated plasma AVP concentrations in spite of lowered plasma osmolalities sufficient in normal subjects to maximally suppress plasma AVP concentrations (44). In experimental cirrhosis, the administration of a V_2 (antidiuretic) AVP antagonist has also been shown to significantly improve water excretion and urinary dilution (45). Moreover, a V_1 (vascular) AVP antagonist has been demonstrated to decrease blood pressure in rats with cirrhosis, over and above the hypotensive effect observed with an angiotensin antagonist (46).

Studies in cirrhotic patients have been undertaken to examine the degree of impairment in water excretion as an index of arterial underfilling secondary to peripheral arterial vasodilation (47). As compared with cirrhotic patients who excreted water normally (more than 80% of a 20-mL/kg oral water load over 5 h), cirrhotic patients with impaired water excretion exhibited higher plasma renin, aldosterone, norepinephrine, and AVP concentrations. These findings are therefore compatible with the neurohumoral compensatory responses secondary to peripheral arterial vasodilation. Although head-out water immersion has been shown to improve sodium and water excretion in decompensated cirrhotic patients in association with significant suppression of the neurohumoral profile of arterial underfilling, the renal water and sodium excretion rates are not normalized (48). Thus, a critical experiment was designed, with hyponatremic, ascitic, cirrhotic patients as their own controls, to examine whether the combination of a systemic vasoconstrictor, norepinephrine, and head-out water immersion would normalize the arterial underfilling and thus renal sodium and water excretion (49). Before this experiment, only liver transplantation had been shown to consistently normalize renal sodium and water excretion in advanced cir-
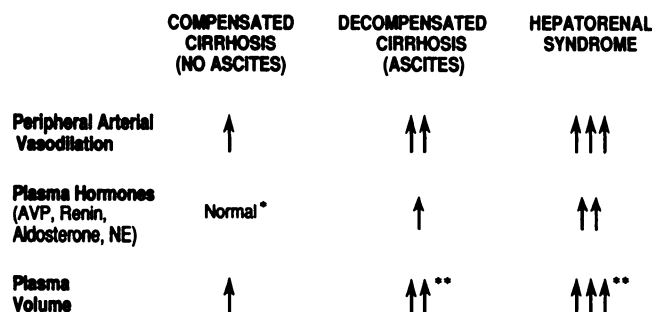
rhosis (50). As with head-out water immersion, the peritoneal jugular LeVeen shunt also improves but does not normalize renal sodium and water excretion in advanced cirrhosis (51). In our acute experiments with the potent systemic vasoconstrictor, norepinephrine, along with head-out water immersion, renal water and sodium excretion were normalized in patients with decompensated cirrhosis (49). Because plasma AVP concentration was not suppressed further with this combined maneuver, as compared with head-out water immersion alone, the normalization of water excretion during the norepinephrine infusion and water immersion was attributed to both suppression of plasma AVP concentration and increased distal fluid delivery. An increase in distal fluid delivery would be expected to accompany an increase in renal perfusion pressure as occurred with this combined maneuver (136/76 mm Hg) when compared with head-out water immersion alone (105/64 mm Hg) (49). The percent increment in water excretion during the combined maneuver designed to normalize arterial circulatory filling in advanced cirrhosis demonstrated a highly significant correlation ($r = 0.97$, $P < 0.01$) with the percent increment in peripheral vascular resistance. These results in decompensated cirrhotic patients therefore provide support for the peripheral arterial vasodilation hypothesis.

As discussed earlier, there is substantial evidence in cirrhosis, as in cardiac failure, that a diminished renal perfusion pressure and increased angiotensin and adrenergic stimulation may not only decrease GFR but also increase proximal tubular sodium reabsorption (52). Taken together, therefore, a decrease in distal sodium delivery would be expected to be a mediator of the impaired aldosterone escape (53) and ANP resistance (54) observed in cirrhosis (Figure 5). As with cardiac failure, the exogenous infusion of ANP may increase urinary cGMP but not sodium excretion, thus supporting a role of diminished distal sodium delivery rather than any ANP receptor down-regulation or inactivation of ANP as a cause of the ANP resistance. In studies in rats with experimental cirrhosis, renal denervation was shown to normalize the natriuretic response to exogenous ANP (55), an observation in support of diminished distal sodium delivery as the mechanism of ANP resistance. As noted earlier, renal denervation has been show to reverse the sodium retention associated with experimental cirrhosis (24). Also, in cirrhotic patients, intraneural recordings have shown increased sympathetic activity to be associated with the presence of ascites and refractoriness to the natriuretic response to ANP (56). Cirrhotic patients with ascites have also been shown to have increased fractional sodium reabsorption as assessed by lithium clearances (57).

In a study by Gregory et al. (58), the administration of the aldosterone antagonist, spironolactone, was shown to be a highly effective means of treating ascites. Thus, as expected with the peripheral arterial vasodilation hypothesis, aldosterone is a major factor in the sodium retention of cirrhosis, particularly because diminished distal sodium delivery limits the renal capacity to escape from the sodium-retaining effect of the hormone. This interpretation is strongly supported by the above-described observation that the combined maneuver of norepinephrine administration and water immersion is associated with an acute reversal of the renal sodium retention in patients with advanced cirrhosis and ascites (49).

Before discussing the progression of the compensatory responses of cirrhosis to maladaptive consequences, it is important to mention the local sodium-retaining effects of arterial vasodilation. In rats with cirrhosis (59) or normal rats receiving the vasodilator, minoxidil (60), the albumin space significantly exceeds the measured plasma volume, a circumstance not seen in control rats. Also, the vasodilated cirrhotic or minoxidil-treated rat has a higher interstitial pressure than do control rats, but an increase in interstitial pressure does not occur with saline expansion. Moreover, in contrast to that in control rats, hyperoncotic albumin increases rather than decreases interstitial pressure, a finding compatible with increased capillary albumin leak in the vasodilated state. Thus, the vasodilated state, whether caused by cirrhosis or an arterial vasodilator, predisposes to interstitial edema because of an increased leak of albumin into the interstitium and a failure of interstitial pressure to increase with saline loading.

A critical area of future research in cirrhosis will be to define the mediator(s) of the associated peripheral arterial vasodilation. The rapidity of the occurrence of this vasodilation suggest a neurohumorally mediated mechanism rather than the establishment of arteriovenous collaterals. The various potential humoral mediators of the peripheral arterial vasodilation in cirrhosis are shown in Figure 8.

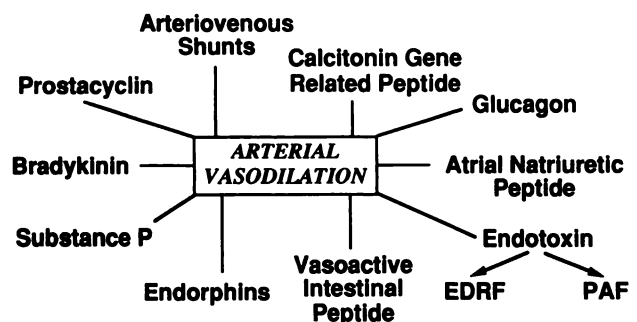The progressive peripheral arterial vasodilation of cirrhosis is associated with systemic and renal neu-

Figure 8. Potential mediators of peripheral arterial vasodilation in cirrhosis. EDRF, endothelium-derived relaxation factor; PAF, platelet-activating factor.

rohumoral events that are initiated to compensate for the arterial underfilling, but they may become maladaptive. Specifically, the renal sodium and water retention of cirrhosis leads to ascites, which predisposes to spontaneous bacterial peritonitis and pulmonary complications. The renal vasoconstriction, which occurs as an integral part of the compensatory constrictor response to systemic arterial vasodilation in cirrhosis, may impair aldosterone escape and progress to the hepatorenal syndrome, even in spite of the compensatory response of the increased renal vasodilator prostaglandins. In this regard, the administration of cyclooxygenase inhibitors, e.g., nonsteroidal anti-inflammatory drugs, may worsen renal function and thereby mimic the hepatorenal syndrome (61). There is also the possibility in cirrhosis that endogenous vasoconstrictors, such as angiotensin, norepinephrine, and AVP, may contribute to the portal hypertension and, thus, the complication of esophageal varices, by constricting the hepatic vein and its tributaries (62).

On the basis of this pathophysiological schema, a treatment strategy may be devised that could decrease the morbidity and mortality in cirrhosis (Figure 9). The vasoconstrictor action of AVP, as mediated by the V_1 receptor, exerts its predominant effect on the splanchnic, muscle, and dermal vascular beds, known sites of vasodilation in cirrhosis. The AVP-mediated decrease in splanchnic blood flow can lower portal pressure and attenuate the esophageal variceal bleeding. The increase in systemic vascular resistance associated with this V_1 vascular effect would also improve renal perfusion pressure, thus enhancing distal sodium delivery and improving aldosterone escape and the natriuretic response to ANP. Renal hemodynamics should also be improved, thus preventing the hepatorenal syndrome. In this context, the infusion of the V_1 agonist, ornipressin, has been shown to improve renal hemodynamics and increase renal sodium and water excretion in decompensated cirrhotic patients (63). Until an orally active, long-acting, nonpeptide V_1 agonist becomes

available, the prophylactic use of the LeVeen shunt might be considered. The removal of the ascites before shunt insertion, prophylactic cephalosporin antibiotics, and the use of a titanium connector at the jugular anastomotic site can significantly decrease the incidence of disseminated intravascular coagulation, shunt and peritoneal infections, and shunt clotting, respectively. We have proposed that a subgroup of cirrhotic patients should be chosen for the prophylactic use of the LeVeen shunt who, in a stable state and without diuretic treatment, excrete less than 20% of a 20-mL/kg water load (64). We monitored seven such cirrhotic patients, and all died of complications within 6 months, except for one patient who received a prophylactic LeVeen shunt and lived in excess of 24 months. Although the use of the LeVeen shunt improves renal function in patients with the hepatorenal syndrome, it did not alter mortality (65) in a prospective randomized study. Thus, future studies of the LeVeen shunt might best consider its prophylactic use in cirrhotic patients with the poorest prognosis but before the development of the hepatorenal syndrome.

PREGNANCY

This odyssey through the milieu intérieur will end by discussing, not the paradoxes of another pathological state such as cardiac failure or cirrhosis, but rather those enigmas of a very normal state, pregnancy. In the first trimester of pregnancy, primary peripheral arterial vasodilation occurs and is accompanied by a rise in cardiac output. These systemic hemodynamic events occur before the blood volume expansion associated with pregnancy (66). It is therefore clear that the peripheral arterial vasodilation of pregnancy is a primary event rather than occurring secondary to blood volume expansion, an interpretation that is also compatible with the consistent lowering of systolic and diastolic blood pressure that occurs in the first trimester of normal pregnancy (67). Moreover, the primary peripheral arterial vasodilation is associated with the neurohumoral response to arterial underfilling including stimulation of the renin-angiotensin-aldosterone axis. In this regard, it is well known that the renin-angiotensin-aldosterone axis is stimulated in pregnancy (68) and in the pregnant baboon, it has been documented that the stimulation of this hormonal axis occurs at the same time as the onset of the primary peripheral arterial vasodilation (69). Moreover, as with cardiac failure and cirrhosis, the increased plasma renin and aldosterone concentrations in pregnancy occur in spite of a 30 to 50% increase in plasma volume.

It has also been shown in human pregnancy that plasma sodium and osmolality are decreased (70). This observation has been termed a "reset osmostat" and is also accompanied by a lowering of the osmotic threshold for thirst (70). Although other causes can-
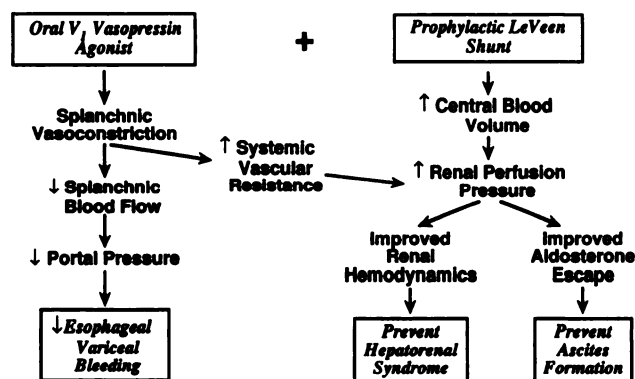
Figure 9. Proposed future treatment strategy for decompensated cirrhosis.

not be excluded, these events associated with pregnancy are compatible with underfilling of the arterial circulation as occurs with primary arterial vasodilation. A study in pregnant rats also demonstrates that the nonosmotic stimulation of AVP release occurs at a plasma volume 40% higher than that in the nonpregnant rat, an additional finding supportive of arterial underfilling in pregnancy (71). In contrast to the increased stimulation of the renin-angiotensin-aldosterone axis and AVP, the plasma norepinephrine measurements in pregnancy have been inconsistent, some demonstrating normal concentrations (72) and others demonstrating increased concentrations (73). In the absence of the underfilling of the arterial circulation, however, the 30 to 50% expansion of plasma volume in pregnancy should be associated with the suppression of sympathetic activity and renin-angiotensin and aldosterone activity, as well as the nonosmotic release of AVP.

The major distinguishing feature between pregnancy and other states of arterial underfilling, such as cardiac failure and cirrhosis, is the absence of renal vasoconstriction. Rather, pregnancy is associated with a 30 to 50% increase in GFR and RGF. The mediator(s) of the increased renal hemodynamics of pregnancy is not known, but it precedes, and therefore is not due to, expansion of blood volume. Moreover, in the pregnant rat, the inhibition of renal prostaglandin synthesis fails to reverse the enhanced renal hemodynamics, the systemic arterial vasodilation, or the pressor resistance to angiotensin (74). Results with an L-arginine analog as an antagonist in the pregnant rat do not support a role for endothelium-derived relaxing factor in the renal or systemic vasodilation of pregnancy (75). Although the uteroplacental arteriovenous shunting no doubt contributes to the systemic vasodilation, it would be expected to cause reflex renal vasoconstriction, not renal vasodilation.

Although most pregnant women exhibit some degree of peripheral edema, the renal handling of acute water and sodium loads in pregnancy is much better than that observed in the advanced stages of cardiac failure or cirrhosis. The role of the 30 to 50% increase in GFR, and, thus, filtered water and sodium, in pregnancy is the most likely factor to account for this improved renal sodium and water handling as compared with that in patients with cardiac failure and cirrhosis. In support of this interpretation is the observation that accelerated sodium retention is a feature of the preeclampsia-eclampsia state of pregnancy, a situation in which the GFR consistently falls by 30 to 50% to levels approximating the values of the nonpregnant state.

On the basis of the pathophysiology of pregnancy involving vasodilation-mediated underfilling of the arterial circulation, we have proposed a pathophysi-
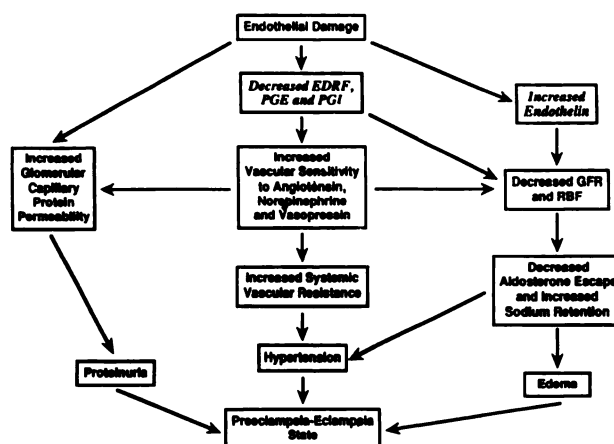

Figure 10. Pathophysiologic schema for preeclampsia and eclampsia. EDRF, endothelium-derived relaxing factor; PG, prostaglandin. From reference 11.

ological schema for preeclampsia and eclampsia (11) (Figure 10). The primary initiating perturbation is suggested to be renal and systemic endothelial damage (11), perhaps by a circulating toxin from the placenta (76). The endothelial damage results in a fall in GFR, and, thus, filtered sodium, which impairs aldosterone escape and causes worsening of edema, a hallmark of the preeclampsia-eclampsia state. The systemic endothelial damage also increases the sensitivity to endogenous vasoconstrictors, which, along with the sodium retention, leads to hypertension, another hallmark of the preeclampsia-eclampsia state. In this regard, increased sensitivity to angiotensin is a known harbinger of the preeclampsia-eclampsia state (77). Last, the increased sensitivity to angiotensin may occur not only at the systemic and renal arteriolar sites but also at the level of the glomerular mesangium. In this regard, angiotensin has been shown to cause proteinuria even in the normal kidney and thus may mediate, at least in part, the proteinuria associated with the preeclampsia-eclampsia state. Hypertension, edema, and proteinuria are the three hallmarks of the preeclampsia-eclampsia state. From this discussion of pregnancy, it is clear that an important area of future research is to identify the renal and systemic vasodilator(s) of pregnancy. Because the vasodilator(s) of pregnancy is more potent in humans than volume expansion, glucocorticoids or protein feeding in raising the steady-state GFR, the therapeutic implications of the discovery of such an agent include not only the preeclampsia-eclampsia state but also the potential treatment of acute and chronic renal failure.

A quote by John Masefield from Lollington Downs, circa 1910, seems appropriate in closing.

What am I, Life? A thing of watery salt
Held in constant cohesion by unresting cells

Which work they know not why, which never halt,
Myself unwitting where there master dwells?

As discussed herein, the master of the milieu inté-
rieur seems to dwell within the arterial circulation.

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