Conferences and Reviews

Paradoxes of Body Fluid Volume Regulation in Health and Disease

A Unifying Hypothesis

ROBERT W. SCHRIER, MD, *and* MICHEL NIEDERBERGER, MD, *Denver, Colorado*

Presented as the Distinguished Lecture at the annual meeting of the Western Association of Physicians, Carmel, California, February 17-18, 1993.

The body's normal homeostasis is maintained by the integrity of the excretory capacity of the kidneys. In advanced cardiac failure, however, the avidity of the renal sodium and water retention contributes to the occurrence of pulmonary congestion and peripheral edema. In patients with advanced cirrhosis, the kidneys again fail to excrete the amounts of sodium and water ingested, thus leading to ascites and peripheral edema. The signals for this renal retention of sodium and water in a patient with cirrhosis must be extrarenal because when the same kidneys are transplanted into persons with normal liver function, renal sodium and water retention no longer occurs; rather, the kidneys maintain normal fluid and electrolyte balance. Excessive sodium and water retention by the kidneys also occurs during pregnancy despite a 30% to 50% increase in plasma volume, cardiac output, and glomerular filtration rate. What are the afferent and efferent signals whereby normal kidneys retain sodium and water so that total extracellular, interstitial, and intravascular volumes expand far beyond those limits observed in normal subjects? These dilemmas are the subject of this review, in which a "unifying hypothesis of body fluid volume regulation" is presented.

(Schrier RW, Niederberger M: Paradoxes of body fluid volume regulation in health and disease—A unifying hypothesis. West J Med 1994; 161:393-408)

The regulation of body fluid volume is important in almost every area of medicine and has been the focus of myriad investigations during this century. When most of life was in a saltwater environment and the species' integument was freely permeable to solutes and water, the compositions of the milieu *intérieur* and *extérieur* were comparable. But when the species moved to land, there was the necessity for a sensitive regulatory system for body fluid volume and composition. The importance of this system was perhaps best emphasized by Claude Bernard when he wrote that "the constancy of the milieu *intérieur* is the condition of free and independent existence."[1]

Various studies in this century examining the regulation and composition of body fluid volume have led to many paradoxical observations, some of which we will summarize here. With the loss of gastrointestinal fluid or hemorrhage, a decrease in extracellular fluid, plasma, and blood volume occurs, and the kidneys respond in what would be viewed as an appropriate manner by retaining sodium and water. But in circumstances such as pregnancy, cirrhosis, and heart failure, extracellular fluid volume, plasma volume, and blood volume are all expanded, and yet the kidneys also retain sodium and water.

Cardiac output has also been examined as the primary regulatory determinant of body fluid volume and renal sodium and water excretion. Cardiac output is decreased with volume depletion associated with diarrhea or hemorrhage, but it is increased in high-output cardiac failure, cirrhosis, and pregnancy; yet, the kidneys retain sodium and water in these three circumstances.

The glomerular filtration rate (GFR) has been proposed as the primary determinant of sodium and water regulation in the body. Thus, with volume depletion, the GFR decreases, and water and sodium retention occurs. The GFR, however, can be increased by 30% to 50% in pregnancy, and yet sodium and water retention occurs and leads to a 30% to 50% expansion of blood volume and extracellular fluid volume.[2] The sensitive regulation of vasopressin (antidiuretic hormone) was shown whereby a 1% to 2% change in extracellular fluid osmolality alters vasopressin release[3]; yet, one of the hallmarks of the edematous disorders is overt hypo-osmolality.[4] Thus, factors other than vasopressin and extracellular

From the Department of Medicine, University of Colorado School of Medicine, Denver, Colorado.

Reprint requests to Robert W. Schrier, MD, Professor and Chair, Dept of Medicine, University of Colorado Health Sciences Center, Box C-281, 4200 E 9th Ave, Denver, CO 80262.

ABBREVIATIONS USED IN TEXT

ANP = atrial natriuretic peptide
cyclic GMP = cyclic guanosine monophosphate
GFR = glomerular filtration rate

fluid osmolality must be involved in regulating renal water excretion, or perhaps there is a "resetting" of the vasopressin osmostat.

The discovery of aldosterone seemed to be a key to renal sodium excretion and thus to extracellular fluid volume regulation.[5] Yet, when excessive amounts of aldosterone are administered to normal persons, only limited sodium retention occurs, and no edema appears—that is, "aldosterone or mineralocorticoid escape" occurs On the other hand, when exogenous aldosterone is administered to patients with cirrhosis or cardiac failure, they do not escape from the sodium-retaining effect of aldosterone, and thus ascites and pulmonary edema, respectively, worsen. The hormone, atrial natriuretic peptide (ANP), was then discovered,[6] and it was thought that sodium retention in heart failure and cirrhosis might be due to a deficiency of this hormone. When the ANP level was measured, however, the plasma concentrations were increased, not decreased, in both heart failure and cirrhosis.[7] Moreover, although exogenous ANP administration causes an increase in urinary flow and sodium excretion in normal subjects, when it is administered to patients with heart failure and cirrhosis, there is a renal resistance to the hormone.[8-10] These examples are just a few of the apparent paradoxes that must be addressed when attempting to understand how body fluid volume and composition are regulated. In this presentation, we propose a unifying hypothesis of volume regulation that addresses these paradoxes. The validity of this hypothesis will be examined in the circumstances of low- and high-output cardiac failure, cirrhosis, and pregnancy.

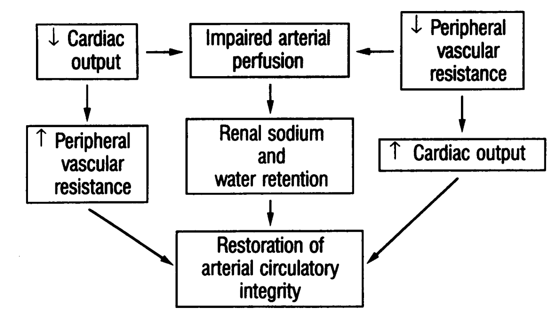

Figure 1.—A decrease in cardiac output or peripheral arterial resistance initiates sodium and water retention in disorders involving edema (from Schrier[18] with permission).

Low-Output Cardiac Failure

At the turn of the century, Starling in Great Britain proposed the backward theory of heart failure.[11] He proposed that in heart failure an increase in venous pressure with fluid transudation from the capillaries into the interstitium leads to a contraction of blood volume, thus triggering renal sodium and water retention. Administering albumin was therefore proposed as a means to treat heart failure. In contrast, it was later proposed that cardiac failure causes primary sodium and water retention that actually leads to an expansion of blood and plasma volumes.[12] This volume expansion then increases venous pressure with subsequent transudation of fluid from capillaries into the interstitium and edema formation. It was therefore proposed that vene-

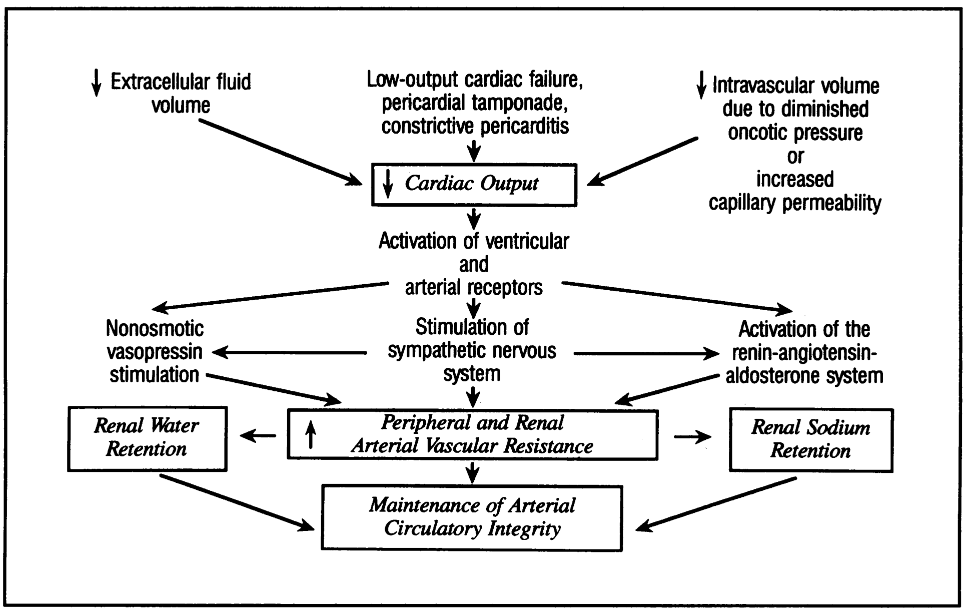

Figure 2.—The sequence of events is shown in which a decrease in cardiac output initiates renal sodium and water retention (from Schrier[15] with permission).

Variable	New York Heart Association Classification II	III	IV
Cardiac index	↓	↓↓	↓↓↓
Plasma hormones (AVP, renin, aldosterone, NE)	Normal	↑	↑↑
Plasma volume	↑	↑↑	↑↑↑

Figure 3.—Neurohumoral and plasma volume responses to progressive cardiac failure are classified according to the New York Heart Association (from Schrier[16] with permission). AVP = arginine vasopressin, NE = norepinephrine

section be considered the treatment of choice for cardiac failure.

Now that most of the body fluid volume compartments can be measured, blood and plasma volumes are known to expand in heart failure. About 85% of the plasma volume is located on the venous side of the circulation and 15% on the arterial side. There is, however, no readily sensitive technique to measure arterial blood volume, which constitutes only 2% of total body fluid. Nevertheless, with this background it is possible to hypothesize that the total plasma volume could be expanded in heart failure if it were mostly on the venous side of the circulation, but underfilling of the arterial circulation could occur due to a decrease in cardiac output. On the other hand, as discussed, cardiac output can be increased in certain circumstances in which sodium and water retention occurs, namely pregnancy, cirrhosis, and high-output heart failure.

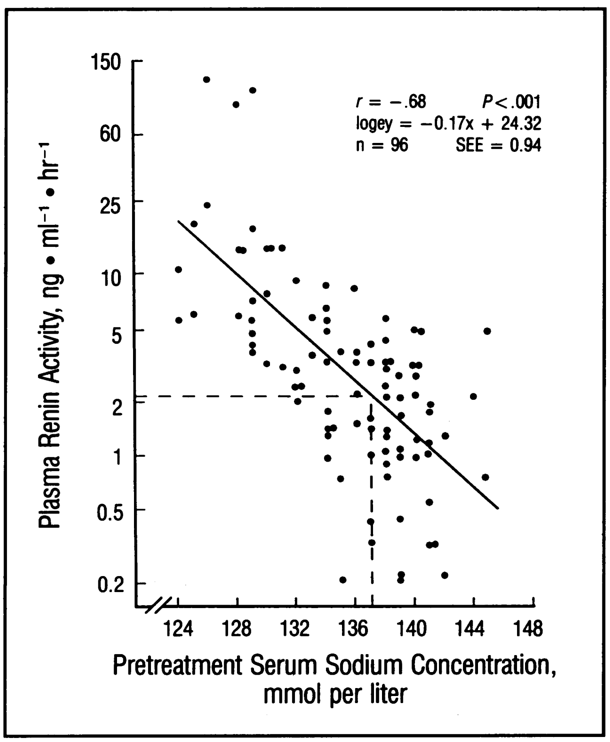

Figure 4.—The relationship is shown between serum sodium concentration and plasma renin activity before vasodilator therapy in 96 patients with severe chronic heart failure (from Lee and Packer[19] with permission). SEE = standard error of the estimate

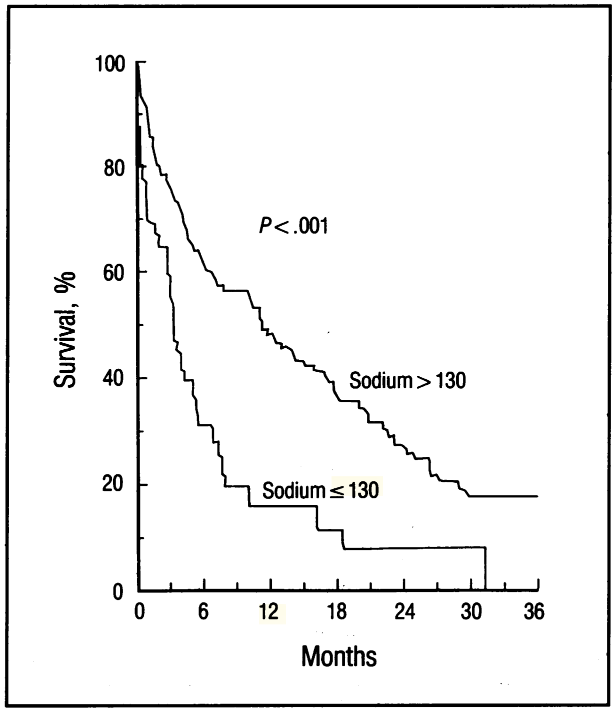

Figure 5.—Kaplan-Meier analysis shows cumulative rates of survival in patients with heart failure stratified into 2 groups based on pretreatment serum sodium concentration—>130 mmol per liter (n=163) versus ≤130 mmol per liter (n=40). Patients with severe hyponatremia had a highly unfavorable long-term prognosis ($P<.001$, Wilcoxon-Breslow) (from Lee and Packer[19] with permission).

If the arterial circulation is the dominant compartment in body fluid volume regulation, there must be a second determinant of arterial underfilling in addition to a diminished cardiac output. This second determinant is proposed to be an increased holding capacity of the arterial circulation as determined by capacitance and arterial vascular resistance. Thus, we propose a unifying hypothesis of body fluid volume regulation that indicates that either a decrease in cardiac output or peripheral arterial vasodilation causes arterial underfilling, and all the subsequent events occur in an attempt to restore arterial circulatory integrity (Figure 1).[13-18] In low cardiac output failure, there would be a secondary increase in peripheral vascular resistance, whereas with arterial vasodilation there is a secondary increase in cardiac output. In both circumstances, renal sodium and water retention occurs in an attempt to restore arterial circulatory integrity.

Virtually all circumstances of sodium and water retention in which the kidneys are normal can be incorpo-

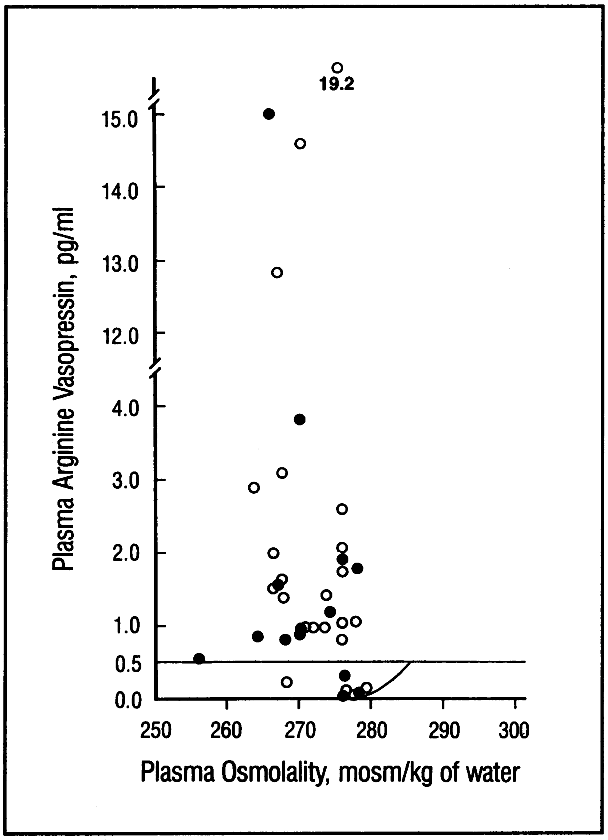

Figure 6.—Plasma arginine vasopressin (AVP) levels are shown in 37 hyponatremic patients with congestive heart failure. ● = patients who never received diuretics before the measurement of AVP levels (n=14); ○ = those patients who received diuretics within 24 hours of blood sampling for AVP measurement (n=23) (from Szatalowicz et al[23] with permission).

rated into this unifying hypothesis. A decrease in cardiac output leading to arterial underfilling may occur with diarrhea, low-output heart failure, pericardial tamponade, constrictive pericarditis, a loss of oncotic pressure due to a protein-losing dermopathy or enteropathy, or with a hypersensitivity reaction causing the loss of colloid from capillaries to the interstitium (Figure 2).[15] The resultant arterial underfilling is sensed by receptors in the ventricle, baroreceptors in the carotid artery and the aortic arch, and renal afferent arterioles. The resultant increased renal sympathetic tone is known to stimulate the renin-angiotensin-aldosterone system and the nonosmotic release of vasopressin. Although less sensitive, the nonosmotic stimulation of vasopressin with arterial underfilling overrides the osmotic regulation of vasopressin release.

As will be discussed, angiotensin and increased adrenergic tone contribute to the impaired escape from the sodium-retaining action of aldosterone, and the nonosmotic release of vasopressin contributes to the water retention. All these responses to arterial underfilling are directed toward the restoration of arterial circulatory integrity.

As cardiac output progressively decreases in a patient with heart failure, a progressive increase in the compensatory neurohumoral profile as assessed by measuring plasma vasopressin, renin, aldosterone, and norepinephrine levels would be expected (Figure 3).[16] Thus, those patients with heart failure with the highest plasma renin activity have the lowest pretreatment plasma sodium concentrations secondary to the stimulation of thirst and the nonosmotic release of vasopressin.[19] Moreover, high plasma renin activity and aldosterone and norepinephrine levels before treatment with diuretics indicate a poor prognosis.[20,21] Patients with this condition have arterial underfilling due to low cardiac indices; the resultant sodium and water retention causes the plasma volume to expand, mostly on the venous side of the circulation.

As shown in Figure 4, pretreatment plasma sodium concentrations in patients with heart failure correlate with plasma renin activities.[19] Moreover, the worst prognosis in a patient with heart failure before treatment occurs with low plasma sodium concentrations.[19] As shown in Figure 5, a pretreatment serum sodium concentration below 130 mmol per liter (130 mEq per liter) in patients with heart failure predicts a worse prognosis than for

TABLE 1.—*Water Excretion and Hemodynamic and Biochemical Characteristics of 2 Groups* of Patients with Heart Failure Classified Along Values of Plasma Vasopressin†*

Clinical Characteristic	*Group I (n=17)*	*Group II (n=8)*	P
Water excretion, %	31.4 ± 3.2	57.1 ± 7.3	<.005
Minimal urinary osmolality, mosm/kg of water	371 ± 36	162 ± 29	<.001
Maximum free water clearance, ml/min	−0.04 ± 0.28	2.03 ± 0.65	<.01
Osmolar clearance, ml/min	1.75 ± 0.2	1.61 ± 0.22	NS
Creatine clearance, ml • min^{-1} • 1.73 m^{-2}	55.4 ± 4.9	53.7 ± 10.4	NS
Cardiac index, liters • min^{-1} • m^{-2}	1.9 ± 0.1	2.47 ± 0.2	<.05
Pulmonary wedge pressure, mm of mercury	30.2 ± 1.4	21.7 ± 1.5	<.02
Right atrial pressure, mm of mercury	13.2 ± 1.2	10.2 ± 1.3	NS
Mean arterial blood pressure, mm of mercury	85.8 ± 2.7	90.8 ± 4.0	NS
Pulse, beats/min	81 ± 3	82 ± 5	NS
Plasma renin activity, ng • ml^{-1} • hr^{-1}	4.4 ± 0.7	1.99 ± 0.4	<.01
Plasma aldosterone, ng/dl	74.1 ± 11.6	10.2 ± 2.1	<.001
Arterial Po_2, mm of mercury	80.3 ± 2.7	80.8 ± 5.9	NS

NS = not significant

*Group I patients had high plasma vasopressin levels (mean, 3 pg/ml); group II patients had undetectable plasma vasopressin levels (<0.5 pg/ml)

† From Bichet et al with permission.[28]

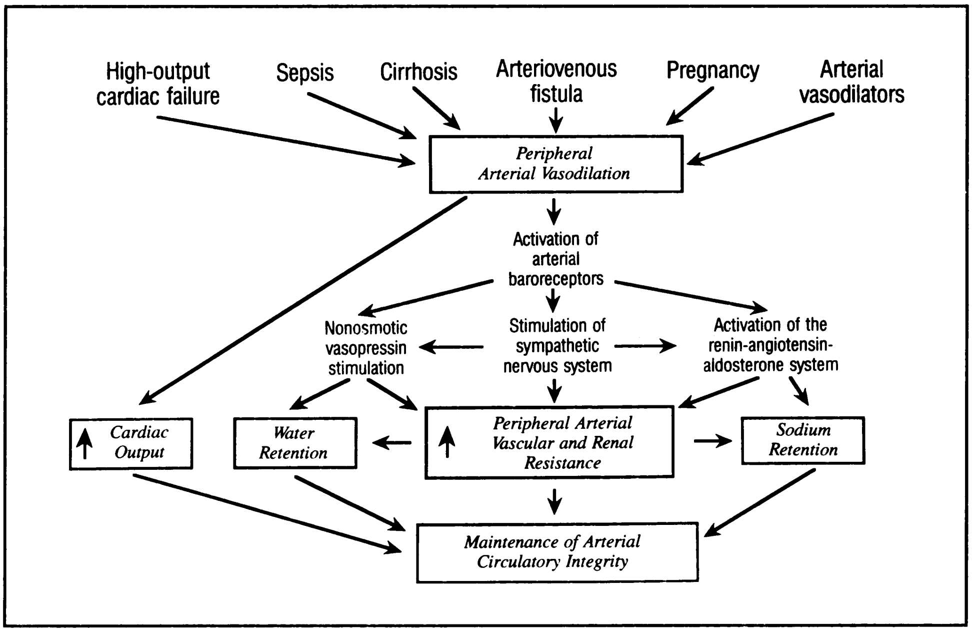

Figure 7.—The sequence of events is shown in which peripheral arterial vasodilation initiates renal sodium and water retention (from Schrier[15] with permission).

those patients with serum sodium concentrations above 130 mmol per liter.

Evidence exists that the increased plasma norepinephrine concentrations in heart failure are a reasonable index of sympathetic activity. Measurements of tritiated secretion rates of norepinephrine in patients with heart failure demonstrated substantially higher secretion rates than in normal persons, whereas the norepinephrine clearance rates were comparable.[22] Thus, increased plasma norepinephrine concentrations in patients with heart failure are primarily due to increased sympathetic activity. As for the role of the sympathetic nervous system in the nonosmotic release of vasopressin, pathways from arterial baroreceptors in the carotid artery and aortic arch travel through the glossopharyngeal and vagus nerves to the nucleus tractus solitarius in the midbrain and then to the hypothalamus, where vasopressin is synthesized in the paraventricular and supraoptic nuclei. With immunohistochemical staining, vasopressin neurons in the paraventricular and supraoptic nuclei can be shown to be interspersed with catecholamine nerve endings. The axons of the vasopressin-synthesizing cell bodies terminate in the posterior pituitary where the hormone is stored and released. This reflex terminates in the nonosmotic release of vasopressin, which is less sensitive but more potent than the osmotic regulation of vasopressin.

Using the vasopressin bioassay, vasopressin was not incriminated in the hyponatremia of heart failure. The bioassay, however, could only detect plasma vasopressin concentrations above 10 pg per ml. When a sensitive radioimmunoassay for vasopressin was developed, it was clear that normal urine concentration and dilution occur in response to plasma vasopressin levels between 0.5 and 4 pg per ml, values that were not detectable with the bioassay. As shown in Figure 6, 30 of 37 patients with heart failure did not have suppressed plasma concentrations of vasopressin, even though they had hypo-osmolarity and hyponatremia; thus, a nonosmotic release of vasopressin occurred in these patients.[23]

TABLE 2.—*Hemodynamics in Rats With High Output Heart Failure**

Hemodynamics	*Control Rats*	*Aorto-caval Fistulae*	P
Mean arterial pressure, mm of mercury	116 ± 9	102 ± 8	<.001
Cardiac output, ml • min^{-1} • 100 grams^{-1} of body weight	39.6 ± 6.7	50.0 ± 9.0	<.001
Peripheral vascular resistance, mm of mercury • min^{-1} • 100 grams^{-1} of body weight	3.11 ± 0.71	1.98 ± 0.37	<.002
Heart weight, grams	1.15 ± 0.13	1.89 ± 0.28	<.001

* Riegger et al with permission.[29]

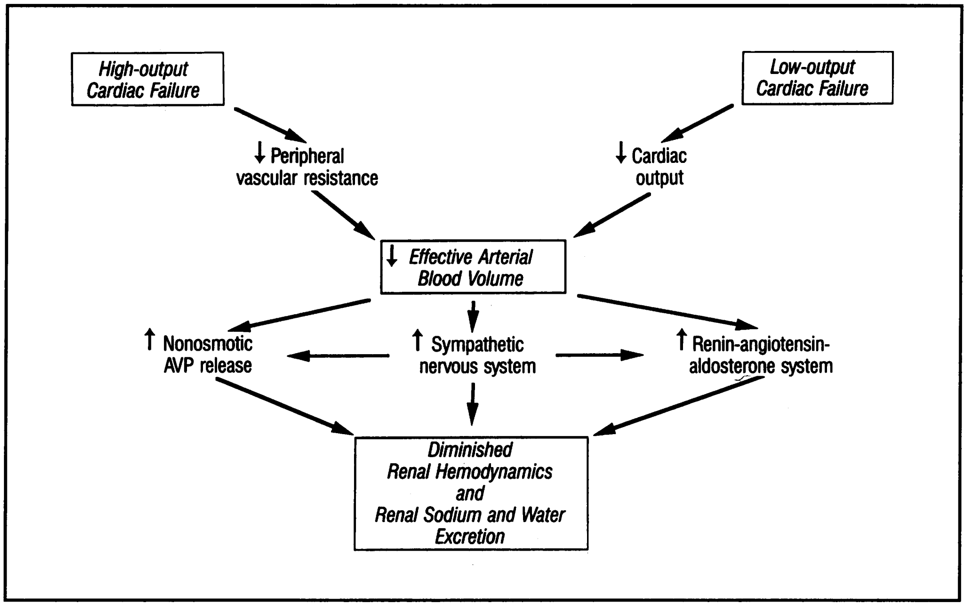

Figure 8.—The mechanisms of high- and low-output cardiac failure are shown. Although the initiating "underfill" event differs in high- and low-output failure, the subsequent pathways leading to renal sodium and water retention are similar (from Schrier[13] with permission). AVP = arginine vasopressin

When complementary DNA probes are used for the preprohormone of vasopressin in the hypothalamus, experimental cardiac failure in animals exhibits increased messenger RNA for vasopressin compared with that in control animals.[24] Thus, both increased nonosmotic vasopressin gene expression and vasopressin release are associated with heart failure.

The V_2 receptor is the antidiuretic receptor for vasopressin, whereas the V_1 receptor is the vascular receptor. In experimental low-output heart failure, impaired diluting ability as demonstrated with an acute water load can be corrected with a V_2 vasopressin antagonist.[25] Thus, in this experimental model of acute heart failure, the nonosmotic release of vasopressin appears to account completely for the impaired water excretion. Orally active nonpeptidic vasopressin antagonists have now been developed in Japan.[26,27]

Patients with hyponatremia in heart failure and with detectable plasma vasopressin concentrations (mean, 3 pg per ml) should have more evidence of arterial underfilling—stimulation of the neurohumoral profile—than patients with heart failure with undetectable

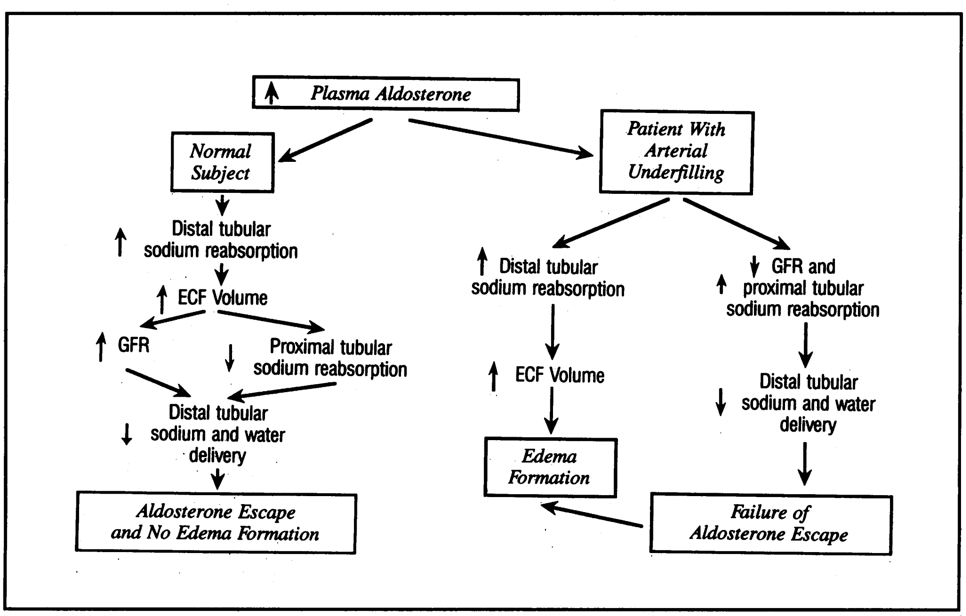

Figure 9.—Events involved in normal (left) and impaired (right) aldosterone escape are shown (from Schrier[15] with permission). ECF = extracellular fluid, GFR = glomerular filtration rate

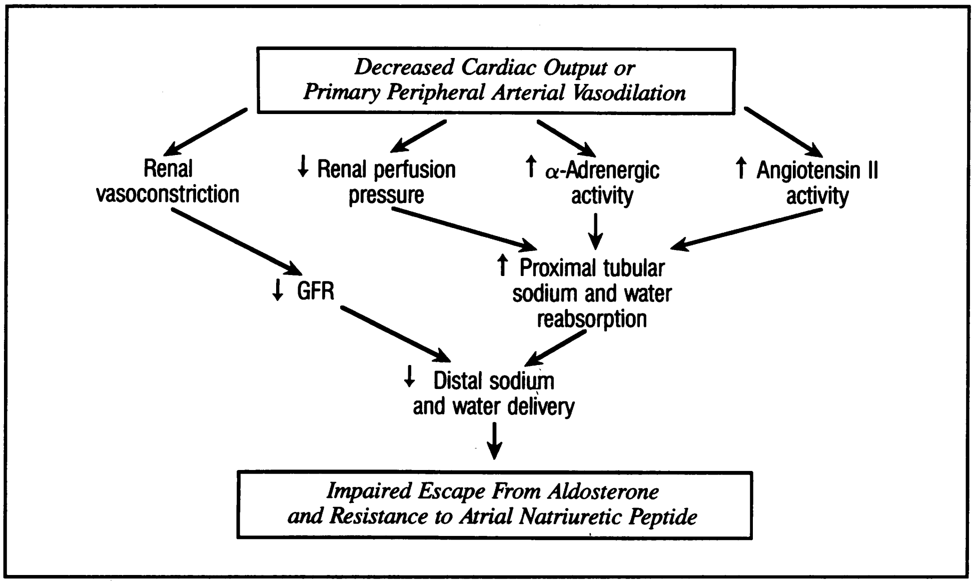

Figure 10.—A decrease in cardiac output or peripheral arterial vasodilation can initiate events that diminish distal sodium delivery, thereby impairing aldosterone escape and causing resistance to atrial natriuretic peptide (from Schrier and Bettor[30] with permission). GFR = glomerular filtration rate

vasopressin levels (<0.5 pg per ml). As shown in Table 1, those patients with evidence of nonosmotic vasopressin release showed significantly lower cardiac indexes, higher pulmonary wedge pressures, and higher plasma renin and aldosterone concentrations.[28] Moreover, when these patients with detectable plasma concentrations of vasopressin were treated with agents to decrease the cardiac afterload, the resultant increase in the cardiac index was associated with improved water excretion and the suppression of plasma and platelet vasopressin.[28]

High-Output Cardiac Failure

In the context of this unifying hypothesis of body fluid volume regulation, the second initiator of arterial underfilling is peripheral arterial vasodilation. Thus, systemic arterial vasodilation should account for the remainder of the circumstances in which sodium and water retention occurs despite normal kidney function. As shown in Figure 7, these clinical states include high-output cardiac failure, sepsis, cirrhosis, large arteriovenous fistulae, pregnancy, and large doses of arterial vasodilators such as minoxidil and hydralazine. The neurohumoral compensatory responses of arterial underfilling due to arterial vasodilation are the same as occurs with arterial underfilling due to a decrease in cardiac output.

In Table 2 are results obtained in an experimental model of high-output cardiac failure.[29] The diminished systemic vascular resistance is associated with an increased cardiac output, cardiac hypertrophy, and activation of the neurohumoral profile of arterial underfilling, namely increased plasma renin activity, aldosterone, norepinephrine, and vasopressin. Thus, one of the paradoxes of body fluid volume regulation can now be ad-

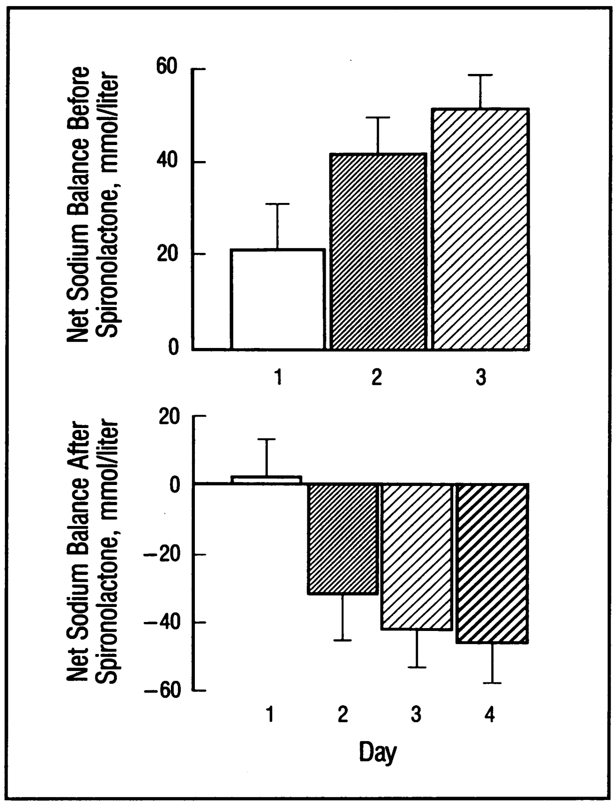

Figure 11.—A reversal of sodium retention by aldosterone antagonism occurs in patients with congestive heart failure. Net positive cumulative sodium balance is seen for the periods before spironolactone is given (**top panel**), and net negative cumulative sodium balance is seen after the initiation of spironolactone therapy (400 mg per day; **bottom panel**). The increase in sodium excretion with spironolactone therapy was significant ($P<.01$) (from Hensen et al[34] with permission).

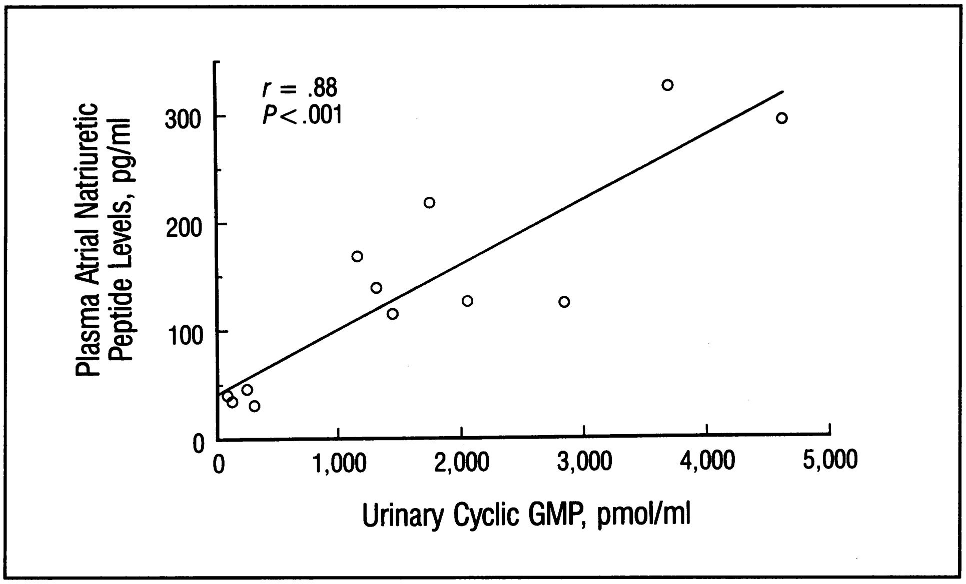

Figure 12.—Plasma atrial natriuretic peptide levels correlate with urinary cyclic guanosine monophosphate (cyclic GMP) levels in patients with heart failure (from Abraham et al[37] with permission).

dressed whereby sodium and water retention can occur in patients in whom cardiac output is low, as with low-output cardiac failure, or high, as with thyrotoxicosis and beriberi. Thus, although the causes of arterial underfilling are different in low- and high-output cardiac failure, the secondary responses to arterial underfilling are comparable (Figure 8).[13]

Aldosterone Escape and Atrial Natriuretic Peptide Resistance in Cardiac Failure

The renal site of action of vasopressin, aldosterone, and ANP is the collecting duct in the terminal portion of the nephron. Either a decrease in the GFR or an increase in proximal tubular reabsorption, or both, can diminish distal sodium and water delivery to the site of action of these hormones in the collecting duct. Because escape from the sodium-retaining effect of aldosterone is dependent on an increased rate of delivery of sodium to the distal nephron, the responses to arterial underfilling may diminish sodium delivery to the collecting duct, thereby explaining the impaired aldosterone escape that is characteristic of arterial underfilling (Figure 9).[15]

In circumstances of arterial underfilling due to either a decrease in cardiac output or primary peripheral arterial vasodilation, a number of factors would lead to a decreased sodium and water delivery to the collecting duct (Figure 10).[30] Advanced heart failure is associated with renal vasoconstriction and a decrease in renal perfusion

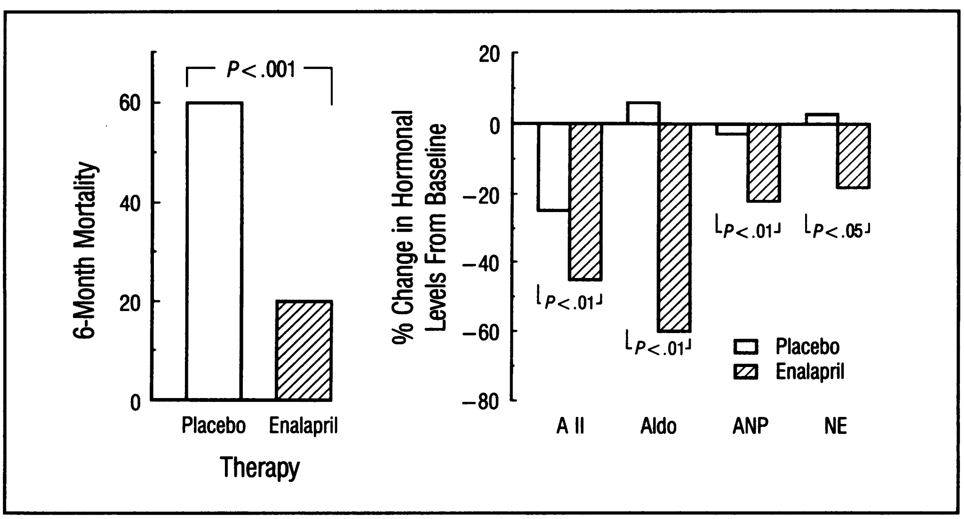

Figure 13.—Enalapril therapy reduces 6-month mortality and hormonal levels in patients with severe congestive heart failure (from Swedberg et al[40] with permission). A II = angiotensin II, Aldo = aldosterone, ANP = atrial natriuretic peptide, NE = norepinephrine

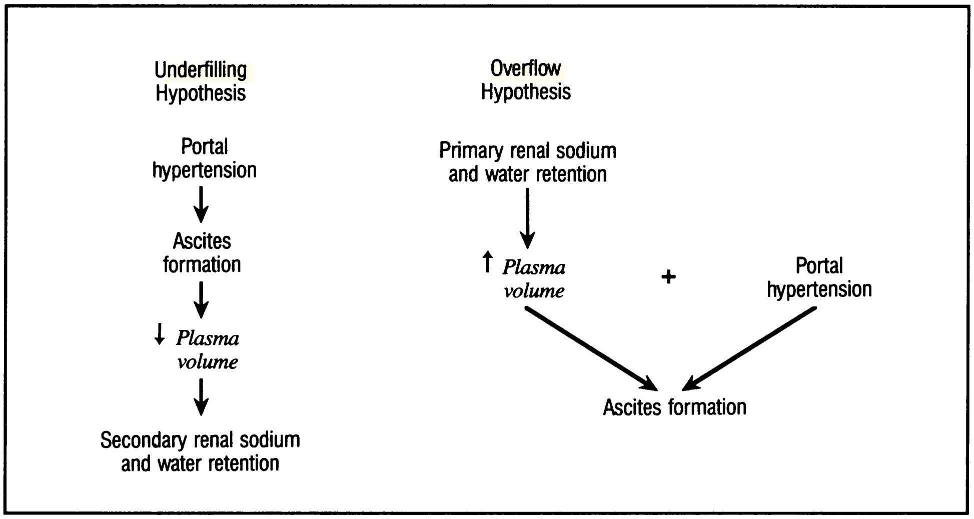

Figure 14.—The characteristics of underfilling (left) and overflow (right) hypotheses of renal sodium and water retention in cirrhosis are shown (from Schrier[17] with permission).

that decrease distal tubular sodium and water delivery. Moreover, direct effects of adrenergic stimulation[31] and angiotensin[32,33] increase proximal tubular sodium and water reabsorption. Thus, impaired aldosterone escape secondary to the consequences of arterial underfilling suggest that aldosterone-mediated sodium retention is important in heart failure. Support for this conclusion derives from the demonstration that large doses of spironolactone (400 mg per day) reverse sodium retention in patients with heart failure (Figure 11).[34]

A resistance to the normal diuretic and natriuretic response to exogenous ANP is another hallmark of heart failure both in experimental models[35,36] and in humans.[8,9] There are several explanations for this ANP resistance: inhibition of renal ANP receptors; immunoreactive plasma ANP that is biologically inactive; or increased neutral endopeptidase activity in the proximal tubule that degrades ANP, thus limiting the hormone delivery to the distal collecting-duct sites of action. These three possibilities for ANP resistance should be associated with decreased activation of the secondary messenger for ANP, namely cyclic guanosine monophosphate (cyclic GMP). When cyclic GMP levels are measured in the urine of patients with heart failure, levels are increased and are correlated with plasma ANP concentrations. When this correlation between plasma ANP and urinary cyclic GMP was studied in patients with heart failure, a linear relationship was found (Figure 12).[37] This last finding supports the concept that diminished renal distal tubular sodium and water delivery is the mechanism of ANP resistance in heart failure, rather than the aforementioned other possibilities.

Because increased renal adrenergic tone is known to increase proximal tubular sodium reabsorption, renal denervation in animals with experimental heart failure might be expected to reverse the ANP resistance. Recent studies have indeed shown that renal denervation reverses the resistance to ANP in experimental heart failure.[38] The first detectable hormonal increase in heart failure is the plasma ANP level, thus raising the possibility that the early onset of sodium retention in cardiac decompensation is delayed by ANP. The following study provides some experimental evidence to support this possibility in early heart failure, even though ANP resistance characterizes advanced heart failure.[39] A comparable decrease in mean arterial pressure was produced in dogs by ventricular tachycardia and thoracic vena caval constriction. Whereas plasma ANP levels rose only with ventricular tachycardia, a decrease in sodium excretion occurred only with caval constriction. The role of the increased ANP concentration with ventricular tachycardia to delay sodium retention was supported by the finding that caval constriction no longer caused sodium retention if exogenous ANP was simultaneously infused to produce a plasma ANP concentration comparable to that observed with ventricular tachycardia.

Variable	Compensated Cirrhosis (no ascites)	Decompensated Cirrhosis (ascites)	Hepatorenal Syndrome
Peripheral arterial vasodilation	↑	↑↑	↑↑↑
Plasma hormones—AVP, renin, aldosterone, NE	Normal	↑	↑↑
Plasma volume	↑	↑↑	↑↑↑

Figure 15.—The "peripheral arterial vasodilation hypothesis" is shown. Normal plasma hormone concentrations indicate relative stimulation in the presence of plasma volume expansion. Hypoalbuminemia may attenuate plasma volume expansion (from Schrier[44] with permission). AVP = arginine vasopressin, NE = norepinephrine

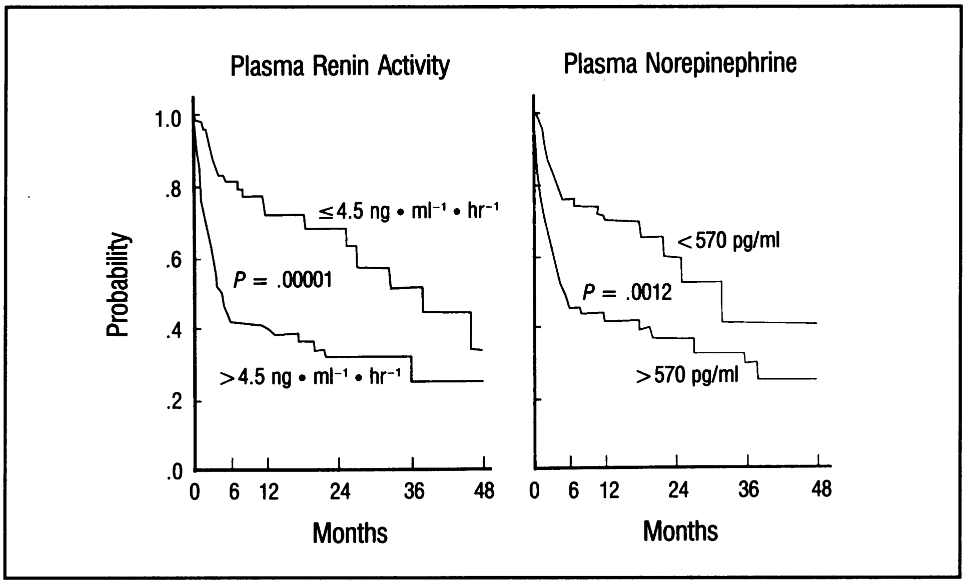

Figure 16.—The plasma renin and norepinephrine concentrations are prognostic indicators in patients with cirrhosis (from Llach[45] with permission).

To summarize, with heart failure, arterial underfilling may occur due to a decrease in cardiac output with myocardial disease or peripheral arterial vasodilation with thyrotoxicosis and beriberi. In the latter circumstance, however, cardiac dysfunction may also accompany the arterial vasodilation. With advanced myocardial disease, the compensatory neurohumoral responses in cardiac failure may become maladaptive. For example, the sodium and water retention may cause pulmonary congestion, whereas the rise in peripheral vascular resistance increases cardiac afterload and myocardial metabolic demand. Results of the CONSENSUS study demonstrate that treatment with angiotensin-converting enzyme inhibitor decreases six-month mortality in association with a decrease in plasma levels of angiotensin, aldosterone, norepinephrine, and ANP (Figure 13).[40]

Cirrhosis

In Figure 14 are shown the two primary hypotheses that have been proposed to explain the sodium and water retention and ascites formation with cirrhosis.[17] With the classic "underfilling hypothesis," portal hypertension causes ascites with an associated decrease in plasma volume that causes secondary renal sodium and water retention.[41] When the plasma volume was found

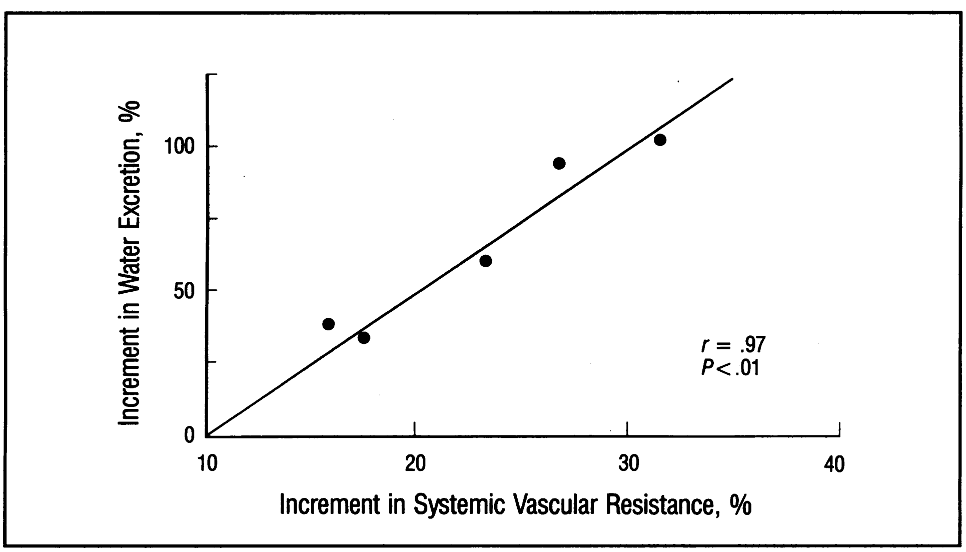

Figure 17.—A correlation is seen between the increase in systemic vascular resistance and the increase in water load excretion from immersion alone to immersion with norepinephrine infusion (from Shapiro et al[52] with permission).

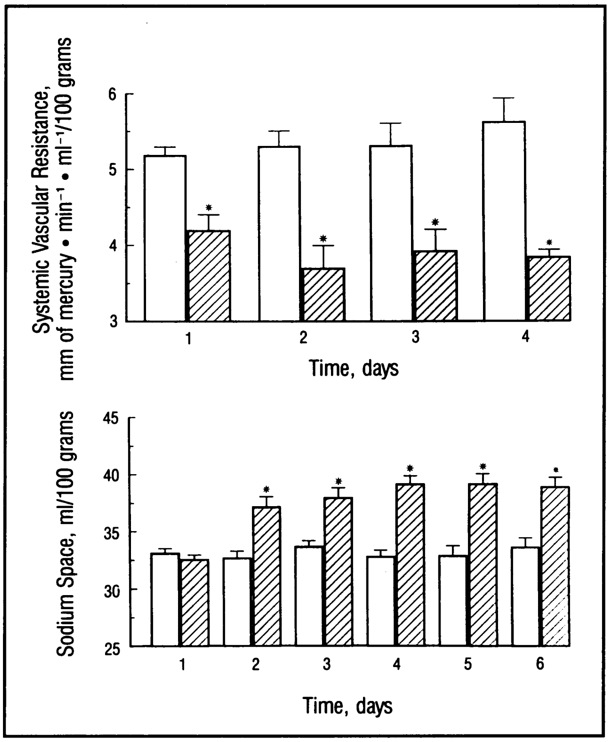

Figure 18.—A temporal relationship is shown between decreased peripheral vascular resistance (**top panel**) and increased sodium space (**bottom panel**) in rats with prehepatic portal hypertension (**shaded bars**) versus sham-operated rats (**white bars**) (from Albillos et al[54] with permission). * = $P<.05$

to be expanded in cirrhosis and this volume expansion antedated the ascites formation, this underfilling hypothesis was no longer tenable. Thus, the "overflow hypothesis" was proposed.[42] This hypothesis proposes that a diseased liver, or some consequence such as an increase in intrahepatic pressure, causes primary sodium and water retention with the expansion of the plasma volume. Ascites then occurs because of the overflow of the plasma volume expansion into the abdominal cavity due to portal hypertension. This overflow hypothesis, however, cannot account for the clinical spectrum of cirrhosis from compensated to decompensated to the hepatorenal syndrome states. This is because the expansion of the plasma volume, on both the venous and arterial sides of the circulation, cannot explain the progressive activation of the neurohumoral profile that characterizes both progressive cirrhosis and arterial underfilling.

The "peripheral arterial vasodilation hypothesis" was therefore proposed.[43] As shown in Figure 15, this hypothesis explains the rise in cardiac output, the fall in mean arterial pressure, and stimulation of the neurohumoral profile of arterial underfilling over the entire clinical spectrum of liver disease.[44] With this hypothesis, patients with cirrhosis with pretreatment hyponatremia and the highest plasma renin, aldosterone, norepinephrine, and vasopressin levels should have the worst prognosis. That is indeed the case. As shown in Figure 16, those patients with cirrhosis with the highest plasma renin and norepinephrine activities have the poorest survival rates.[43]

Using a complementary DNA probe for the preprohormone, levels of the hypothalamic messenger RNA for vasopressin were shown to be increased in experimental cirrhosis.[44] Thus, in cirrhosis, there is not only an increased release of vasopressin from the pituitary, but also an enhanced hypothalamic biosynthesis occurs, as is also characteristic of heart failure.

It is clear that patients with cirrhosis differ in their degree of arterial underfilling and may be separated by their capacity to excrete a water load of 20 ml per kg of body weight. Those patients with cirrhosis who have impaired water excretion demonstrate more evidence of arterial underfilling than patients with cirrhosis who normally excrete the same 20-ml-per-kg water load.[47] Nonexcreting patients have lower plasma sodium concentrations, higher urinary osmolalities, and higher plasma renin, aldosterone, norepinephrine, and vasopressin concentrations than patients who excrete a water load normally.[47] In 26 patients with cirrhosis, there was a significant correlation between plasma norepinephrine, as an index of sympathetic activity, and plasma vasopressin and renin activity. The administration of a V_2 vasopressin antagonist has been shown to improve water excreting and diluting ability in experimental cirrhosis,[48] thus incriminating the nonosmotic release of vasopressin in water retention. There is also a role of the V_1 vasopressin receptor in maintaining blood pressures in patients with cirrhosis.[49] In experimental cirrhosis, the V_1 vasopressin vascular antagonist causes a fall in blood pressure, indicating that vasopressin, as well as angiotensin and the sympathetic nervous system, is an important factor in maintaining arterial circulatory integrity in cirrhosis.

In these same 26 patients with cirrhosis studied on a constant sodium intake, there was a significant positive correlation between plasma renin activity and plasma norepinephrine levels and a negative correlation between urinary sodium excretion and plasma norepinephrine levels.[47] These results are consonant with a role of angiotensin and adrenergic stimulation in decreasing sodium delivery to the distal nephron in cirrhosis, as occurs in heart failure. The sodium and water retention in cirrhosis clearly is also due to extrarenal events, as the kidneys of patients with the hepatorenal syndrome have been shown to be no longer retaining sodium when transplanted to recipients with normal livers,[50] or when normal livers are transplanted into these patients with the hepatorenal syndrome.[51]

On this background, a combined maneuver of head-out water immersion and administering exogenous norepinephrine to reverse arterial vasodilation was studied in hyponatremic, ascitic patients with cirrhosis in an effort to reverse the sodium and water retention.[52] The results demonstrated that this maneuver returned sodium and water excretion to normal in these patients with ad-

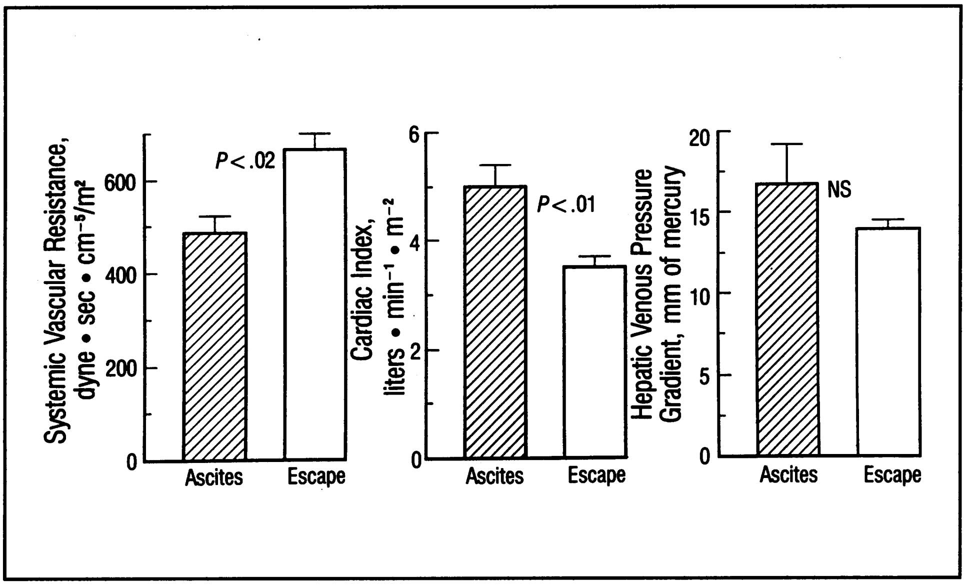

Figure 19.—Baseline systemic hemodynamic measurements and hepatic venous pressure gradient are shown, as an index of portal pressure, in a group of 19 cirrhotic patients without a history of sodium retention treated with mineralocorticoids (from La Villa et al[55] with permission). Escape (n = 15): patients who showed a mineralocorticoid escape phenomenon and did not develop ascites; Ascites (n = 4): patients in whom persistent sodium retention and ascites developed during mineralocorticoid administration; NS = not significant

vanced cirrhosis, thus supporting the concept that arterial underfilling due to arterial vasodilation in the splanchnic and other vascular beds is the cause of sodium and water retention. Further support from these results for the peripheral arterial vasodilation hypothesis was the finding of a strong correlation between the increment in water excretion and that in systemic vascular resistance (Figure 17). As in heart failure, there is evidence for an important role of aldosterone in the sodium retention that occurs in cirrhosis. Investigators showed that 16 of 21 patients with cirrhosis treated over three to four weeks with large doses of the competitive aldosterone antagonist spironolactone had resolution of their ascites, in contrast to only 4 of 22 matched, untreated patients with cirrhosis.[53]

Studies in rats with portal hypertension due to portal vein constriction provide information about the temporal relationship between portal hypertension, splanchnic vasodilation, and sodium retention.[54] As shown in Figure 18, a fall in systemic vascular resistance

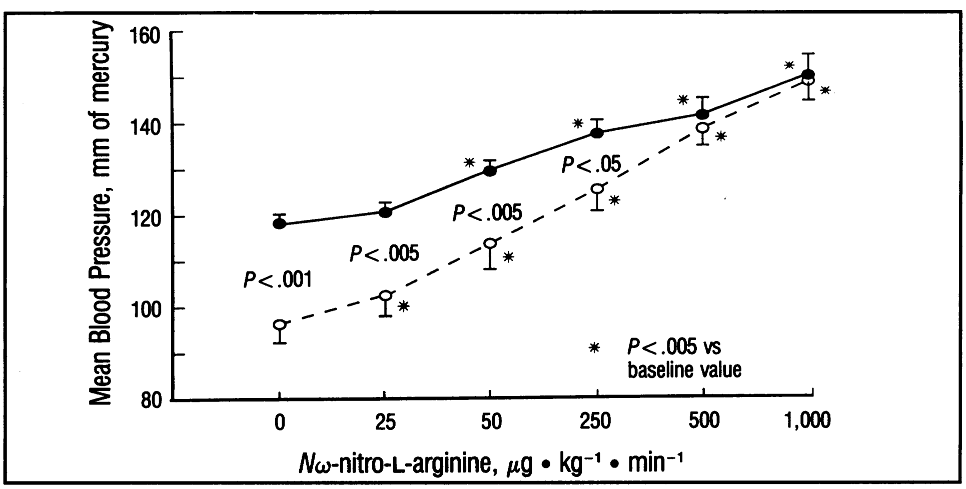

Figure 20.—Mean blood pressures are shown under basal conditions and after the administration of sustained, increasing doses of *N*ω-nitro-L-arginine in cirrhotic (-o-) and control (-•-) rats. Data are given as mean ± standard error of the mean. *P* values given in the figure are those obtained when comparing cirrhotic and control rats (from Clària et al[56] with permission). * = *P*<.005 versus baseline values

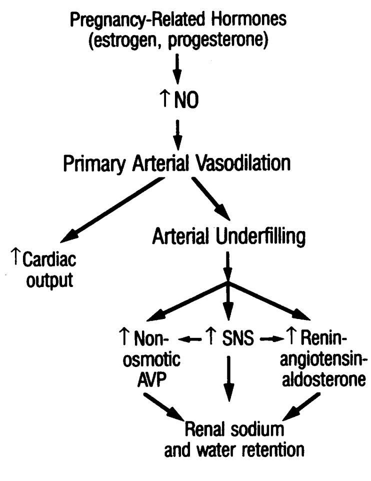

Figure 21.—The peripheral arterial vasodilation hypothesis in pregnancy is illustrated. AVP = arginine vasopressin, NO = nitric oxide, SNS = sympathetic nervous system

occurs within 24 hours after the onset of acute portal hypertension, whereas a rise in total body sodium first occurs within 48 hours after the onset of portal hypertension. These results are compatible with arterial underfilling due to arterial vasodilation initiating sodium retention in association with portal hypertension.

Studies in patients with compensated cirrhosis without ascites provide further important information about the mechanisms of sodium retention and ascites formation. These studies examined the capacity to escape from the sodium-retaining effect of mineralocorticoid hormone. In support of the peripheral arterial vasodilation hypothesis, ascites developed in those patients who did not have mineralocorticoid escape, and they had lower systemic vascular resistances and higher cardiac outputs than those patients who had mineralocorticoid escape (Figure 19).[55] No difference occurred in the hepatic venous pressure gradient, as an index of portal hypertension and intrahepatic pressure, between these two groups of cirrhotic patients. In vasodilated patients, plasma renin activity was also not suppressed, and their plasma ANP levels were not increased during mineralocorticoid administration.

What causes the systemic vasodilation in cirrhosis? There is now substantial evidence suggesting that at least one factor in the vasodilation associated with cirrhosis is the induction of nitric oxide synthase in either vascular smooth muscle, endothelial cells, or both. Administering L-arginine analogues, which block nitric oxide synthase, has been shown to increase the mean arterial pressure in a dose-response manner so that with maximal doses there is no difference in arterial pressures between control and cirrhotic animals (Figure 20).[56] Because plasma endotoxin concentrations have been shown to be increased in cirrhosis[57] and endotoxin may induce nitric oxide synthase in vascular smooth muscle,[58,59] these results support a role of nitric oxide—that is, endothelium-derived relaxing factor—in the vasodilation associated with cirrhosis. Other vasodilators, however, as well as portosystemic shunting, may also be involved in the later stages of cirrhosis.[60-69]

A resistance in ANP has also been shown to occur in cirrhosis in a manner similar to that in cardiac failure. There also does not seem to be any defect in the biologic activity of ANP receptor activation because exogenous ANP has been shown to increase urinary cyclic GMP levels even in those cirrhotic patients whose urinary flow or sodium excretion rates did not increase in response to increasing doses of exogenous ANP.[70,71] Evidence for diminished distal sodium and water delivery due to the consequences of arterial vasodilation (Figure 10) as a cause for the ANP resistance is the finding that this phenomenon can be reversed by renal denervation in experimental cirrhosis in rats.[72]

Local effects of arterial vasodilation also contribute to sodium and water retention in cirrhosis and other vasodilated states. Specifically, albumin distribution space and interstitial compliance have been shown to be increased in both cirrhotic rats[73] and normal rats treated with the arterial vasodilator minoxidil.[74] Thus, a relative increase in interstitial oncotic pressure and a decrease in interstitial hydrostatic pressure with the dilation of precapillary arteriolar sphincters would be expected to predispose to edema formation.

To summarize, peripheral arterial vasodilation in cirrhosis causes arterial underfilling and adaptive neurohumoral responses that can become maladaptive in extreme circumstances. Specifically, the resultant ascites formation predisposes to spontaneous bacterial peritonitis, the renal vasoconstriction predisposes to the hepatorenal syndrome, and the increased splanchnic vasodilation and flow are major contributors to the portal hypertension and esophageal varices, all of which combine to increase morbidity and mortality in patients with cirrhosis. A therapeutic strategy to reverse these extrahepatic consequences of cirrhosis could be designed to attenuate these causes of morbidity and mortality in this disorder. Administering an orally active, long-acting V_1 agonist, β-blockers, or somatostatin to decrease splanchnic flow and an early prophylactic LeVeen peritoneovenous shunt should decrease the arterial underfilling in cirrhosis.[75] This approach should then suppress the neurohumoral responses to arterial underfilling and thereby prevent the hepatorenal syndrome; allow for aldosterone escape, thus preventing ascites formation and spontaneous bacterial peritonitis; and decrease splanchnic flow with a lowering of the portal pressure, thus diminishing the morbidity and mortality of esophageal variceal bleeding.

Pregnancy

Pregnancy is associated with a 30% to 50% increase in extracellular fluid, plasma, and blood volume and a 30% to 50% increase in cardiac output, GFR, and renal blood flow. Primary renal sodium and water retention

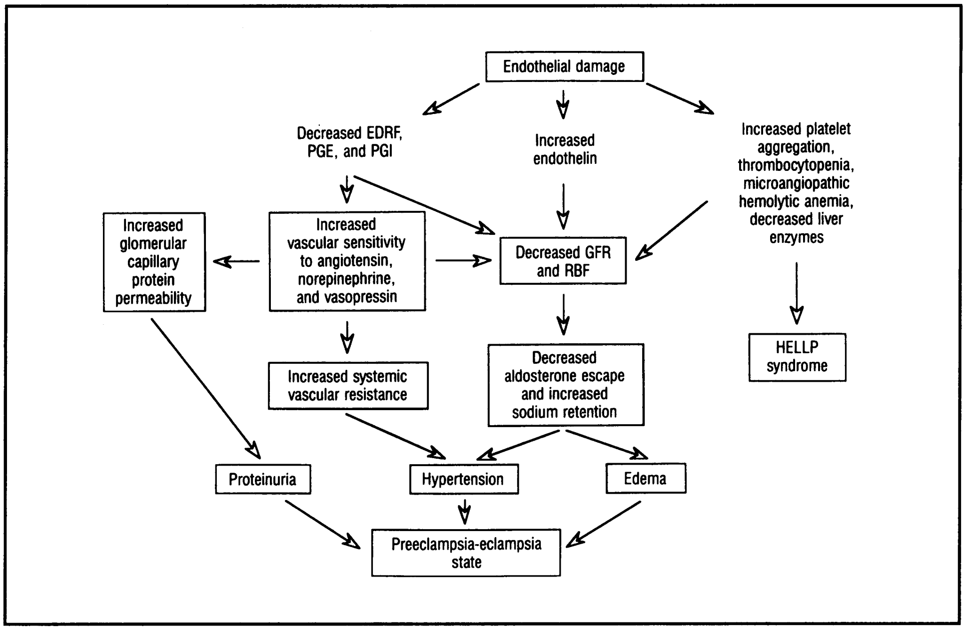

Figure 22.—The pathophysiologic schema for preeclampsia and eclampsia is shown (from Abraham et al[37] with permission). EDRF = endothelium-derived relaxing factor; GFR = glomerular filtration rate; HELLP = hemolysis, elevated liver enzymes, and low platelet count; PGE = prostaglandin E; PGI = prostaglandin I; RBF = renal blood flow

has been suggested to account for these changes associated with normal pregnancy. Several important factors, however, suggest that primary arterial vasodilation causing arterial underfilling with secondary sodium and water excretion occurs in pregnancy. For example, a fall in systolic and diastolic blood pressures occurs in the first trimester of pregnancy despite an increase in the blood volume.[76] The renin-angiotensin-aldosterone axis is activated early in pregnancy, an effect also expected with arterial underfilling due to peripheral arterial vasodilation,[77] whereas primary volume expansion would be expected to suppress these hormones. The increase in GFR and renal blood flow in pregnancy precedes the expansion of the blood volume,[78] thus suggesting primary renal vasodilation. Additional important findings in pregnancy are the "resetting" of the vasopressin-osmoreceptor[79] and the volume depletion-vasopressin relationships[80] in a direction suggestive of arterial underfilling due to systemic arterial vasodilation.

Emerging evidence suggests that nitric oxide mediates the peripheral arterial vasodilation of pregnancy. Long-term blockade of nitric oxide synthase with nitro-L-arginine methylester is associated with a return to normal of mean arterial pressures in pregnant rats compared with controls.[81] Moreover, in the same study, the administration of an L-arginine bolus was associated with a substantially greater fall in mean arterial pressures in pregnant than in nonpregnant rats. Hormones known to increase in pregnancy, such as estrogen and progesterone, have been shown to induce nitric oxide synthase in in vitro experiments.[82,83] Further support for a role for nitric oxide in the vasodilation of pregnancy derives from the correlation between urinary cyclic GMP, the secondary messenger of nitric oxide, and urinary nitrate excretion, a metabolite of nitric oxide.[84,85] Recent preliminary studies from our laboratory also have shown an effect of nitro-L-arginine methylester on the response of aortic rings without endothelium to phenylephrine in pregnant but not nonpregnant rats. The resistance to angiotensin, norepinephrine, and vasopressin that characterizes normal pregnancy has also been shown to be reversed by the blockade of nitric oxide synthase.[86] In Figure 21 is shown the hypothesis whereby nitric oxide-induced arterial vasodilation initiates arterial underfilling in pregnancy. Moreover, endothelial damage in pregnancy, perhaps due to a circulating toxin released from an ischemic placenta, may initiate the events leading to the preeclampsia-eclampsia state.[87] These events are shown in Figure 22, including increased sensitivity to pressor hormones, a decrease in the GFR and renal blood flow, and failure to escape from the sodium-retaining effect of aldosterone, all combining to cause proteinuria, hypertension, and edema—the hallmarks of the preeclampsia-eclampsia state.[88]

In conclusion, to quote John Masefield: "What is life, the thing of watery salt held in cohesion by unresting cells which work, they know not why, which never halt myself unwitting where their master dwells." Our unifying hypothesis of body fluid volume regulation indicates that "the master" dwells in the arterial circulation.

REFERENCES

1. Bernard C: Leçons sur les phénomènes de la vie communs aux animaux et aux végétaux. Paris, France, JB Baillière et Fils, 1885

2. Briner VA, Berl T, Schrier RW: Renal function in pregnancy, *In* Schrier RW (Ed): Renal and Electrolyte Disorders, 4th edition. Boston, Mass, Little, Brown, 1992, pp 635-680

3. Verney EB: The antidiuretic hormone and the factors which determine its release. Proc R Soc Lond Ser B 1947; 135:25-106

4. Anderson RJ, Chung HM, Kluge R, Schrier RW: Hyponatremia: A prospective analysis of its epidemiology and the pathogenetic role of vasopressin. Ann Intern Med 1985; 102:164-168

5. Luetscher JA, Johnson BB, Axelrad BJ, Cater JE, Sala G: Apparent identity of electrocortin with the sodium retaining corticoid extracted from human urine (Abstr). J Clin Endocrinol 1954; 14:812

6. De Bold AJ, Borenstein HB, Veress AT, Sonnenberg H: A rapid and potent natriuretic response to intravenous injection of atrial myocardial extract in rats. Life Sci 1981; 28:89-94

7. Shenker Y, Sider RS, Ostafin EA, Grekin RJ: Plasma levels of immunoreactive atrial natriuretic factor in healthy subjects and in patients with edema. J Clin Invest 1985; 76:1684-1687

8. Cody RJ, Atlas SA, Laragh JH, et al: Atrial natriuretic factor in normal subjects and heart failure patients—Plasma levels and renal, hormonal, and hemodynamic responses to peptide infusion. J Clin Invest 1986; 78:1362-1374

9. Goy JJ, Waeber B, Nussberger J, et al: Infusion of atrial natriuretic peptide to patients with congestive heart failure. J Cardiovasc Pharmacol 1988; 12:562-570

10. Petrillo A, Scherrer U, Gonvers JJ, et al: Atrial natriuretic peptide administered as intravenous infusion or bolus injection to patients with liver cirrhosis and ascites. J Cardiovasc Pharmacol 1988; 12:279-285

11. Starling EH: Fluids of Body—The Herter Lectures (New York 1908). Chicago Ill, Keener, 1909

12. Stead EAJ, Ebert RV: Shock syndrome produced by failure of heart. Arch Intern Med 1942; 69:369-383

13. Schrier RW: Pathogenesis of sodium and water retention in high-output and low-output cardiac failure, nephrotic syndrome, cirrhosis, and pregnancy (pt 1). N Engl J Med 1988; 319:1065-1072

14. Schrier RW: Pathogenesis of sodium and water retention in high-output and low-output cardiac failure, nephrotic syndrome, cirrhosis, and pregnancy (2). N Engl J Med 1988; 319:1127-1134 [published erratum in N Engl J Med 1989; 320:676]

15. Schrier RW: Body fluid volume regulation in health and disease: A unifying hypothesis. Ann Intern Med 1990; 113:155-159

16. Schrier RW: An odyssey into the milieu intérieur: Pondering the enigmas. J Am Soc Nephrol 1992; 2:1549-1559

17. Schrier RW: A unifying hypothesis of body fluid volume regulation—The Lilly Lecture 1992. J R Coll Physicians Lond 1992; 26:295-306

18. Schrier RW: Effective blood volume revisited: Pathogenesis of edematous disorders, *In* Davison JM (Ed): Nephrology. London, England, Baillière Tindall, 1988, pp 663-675

19. Lee WH, Packer M: Prognostic importance of serum sodium concentration and its modification by converting-enzyme inhibition in patients with severe chronic heart failure. Circulation 1986; 73:257-267

20. Dzau VJ, Colucci WS, Hollenberg NK, Williams GH: Relation of the renin-angiotensin-aldosterone system to clinical state in congestive heart failure. Circulation 1981; 63:645-651

21. Levine TB, Francis GS, Goldsmith SR, Simon AB, Cohn JN: Activity of the sympathetic nervous system and renin-angiotensin system assessed by plasma hormone levels and their relation to hemodynamic abnormalities in congestive heart failure. Am J Cardiol 1982; 49:1659-1666

22. Abraham WT, Hensen J, Schrier RW: Elevated plasma noradrenaline concentrations in patients with low-output cardiac failure: Dependence on increased noradrenaline secretion rates. Clin Sci 1990; 79:429-435

23. Szatalowicz VL, Arnold PE, Chaimovitz C, Bichet D, Berl T, Schrier RW: Radioimmunoassay of plasma arginine vasopressin in hyponatremic patients with congestive heart failure. N Engl J Med 1981; 305:263-266

24. Kim JK, Michel JB, Soubrier F, Durr J, Corvol P, Schrier RW: Arginine vasopressin gene expression in chronic cardiac failure in rats. Kidney Int 1990; 38:818-822

25. Ishikawa S, Saito T, Okada K, Tsutsui K, Kuzuya T: Effect of vasopressin antagonist on water excretion in inferior vena cava constriction. Kidney Int 1986; 30:49-55

26. Yamamura Y, Ogawa H, Yamashita H, et al: Characterization of a novel aquaretic agent, OPC-31260, as an orally effective, nonpeptide vasopressin V_2 receptor antagonist. Br J Pharmacol 1992; 105:787-791

27. Yamamura Y, Ogawa H, Chihara T, et al: OPC-21268, An orally effective, nonpeptide vasopressin V_1 receptor antagonist. Science 1991; 252:572-574

28. Bichet DG, Kortas C, Mettauer B, et al: Modulation of plasma and platelet vasopressin by cardiac function in patients with heart failure. Kidney Int 1986; 29:1188-1196

29. Riegger GA, Liebau G, Bauer E, Kochsiek K: Vasopressin and renin in high output heart failure of rats: Hemodynamic effects of elevated plasma hormone levels. J Cardiovasc Pharmacol 1985; 7:1-5

30. Schrier RW, Better OS: Pathogenesis of ascites formation: Mechanism of impaired aldosterone escape in cirrhosis. Eur J Gastrohepatol 1991; 3: 721-729

31. Bello-Reuss E: Effect of catecholamines on fluid reabsorption by the isolated proximal convoluted tubule. Am J Physiol 1980; 238:F347-F352

32. Schuster VL, Kokko JP, Jacobson HR: Angiotensin II directly stimulates sodium transport in rabbit proximal convoluted tubules. J Clin Invest 1984; 73:507-515

33. Liu FY, Cogan MG: Angiotensin II: A potent regulator of acidification in the rat early proximal convoluted tubule. J Clin Invest 1987; 80:272-275

34. Hensen J, Abraham WT, Durr JA, Schrier RW: Aldosterone in congestive heart failure: Analysis of determinants and role in sodium retention. Am J Nephrol 1991; 11:441-446

35. Koepke JP, DiBona GF: Blunted natriuresis to atrial natriuretic peptide in chronic sodium-retaining disorders. Am J Physiol 1987; 252:F865-F871

36. Riegger GA, Elsner D, Kromer EP, et al: Atrial natriuretic peptide in congestive heart failure in the dog: Plasma levels, cyclic guanosine monophosphate, ultrastructure of atrial myoendocrine cells, and hemodynamic, hormonal, and renal effects. Circulation 1988; 77:398-406

37. Abraham WT, Hensen J, Kim JK, et al: Atrial natriuretic peptide and urinary cyclic guanosine monophosphate in patients with chronic heart failure. J Am Soc Nephrol 1992; 2:1697-1703

38. DiBona GF, Herman PJ, Sawin LL: Neural control of renal function in edema-forming states. Am J Physiol 1988; 254:R1017-R1024

39. Lee ME, Miller WL, Edwards BS, Burnett JC Jr: Role of endogenous atrial natriuretic factor in acute congestive heart failure. J Clin Invest 1989; 84:1962-1966

40. Swedberg K, Eneroth P, Kjekshus J, Wilhelmsen L: Hormones regulating cardiovascular function in patients with severe congestive heart failure and their relation to mortality—CONSENSUS Trial Study Group. Circulation 1990; 82:1730-1736

41. Papper S: The role of the kidney in Laennec's cirrhosis of the liver. Medicine (Baltimore) 1958; 37:299-316

42. Lieberman FL, Denison EK, Reynolds TB: The relationship of plasma volume, portal hypertension, ascites, and renal sodium retention in cirrhosis: The overflow theory of ascites formation. Ann N Y Acad Sci 1970; 170:202-212

43. Schrier RW, Arroyo V, Bernardi M, Epstein M, Henriksen JH, Rodés J: Peripheral arterial vasodilation hypothesis: A proposal for the initiation of renal sodium and water retention in cirrhosis. Hepatology 1988; 8:1151-1157

44. Schrier RW (Ed): Manual of Nephrology, 3rd edition. Boston, Mass, Little, Brown, 1990, pp 1-19

45. Llach J, Gines P, Arroyo V, et al: Prognostic value of arterial pressure, endogenous vasoactive systems, and renal function in cirrhotic patients admitted to the hospital for the treatment of ascites. Gastroenterology 1988; 94:482-487

46. Kim JK, Summer SN, Howard RL, Schrier RW: Vasopressin gene expression in rats with experimental cirrhosis. Hepatology 1993; 17:143-147

47. Bichet DG, Van Putten VJ, Schrier RW: Potential role of increased sympathetic activity in impaired sodium and water excretion in cirrhosis. N Engl J Med 1982; 307:1552-1557

48. Clària J, Jiménez W, Arroyo V, et al: Blockade of the hydro-osmotic effect of vasopressin normalizes water excretion in cirrhotic rats. Gastroenterology 1989; 97:1294-1299

49. Clària J, Jiménez W, Arroyo V, et al: Effect of V_1-vasopressin receptor blockade on arterial pressure in conscious rats with cirrhosis and ascites. Gastroenterology 1991; 100:494-501

50. Koppel MH, Coburn JW, Mims MM, Goldstein H, Boyle JD, Rubini ME: Transplantation of cadaveric kidneys from patients with hepatorenal syndrome—Evidence for the functional nature of renal failure in advanced liver disease. N Engl J Med 1969; 280:1367-1371

51. Iwatsuki S, Popovtzer MM, Corman JL, et al: Recovery from 'hepatorenal syndrome' after orthotopic liver transplantation. N Engl J Med 1973; 289:1155-1159

52. Shapiro MD, Nicholls KM, Groves BM, et al: Interrelationship between cardiac output and vascular resistance as determinants of effective arterial blood volume in cirrhotic patients. Kidney Int 1985; 28:206-211

53. Gregory PB, Broekelschen PH, Hill MD, et al: Complications of diuresis in the alcoholic patient with ascites: A controlled trial. Gastroenterology 1977; 73:534-538

54. Albillos A, Colombato LA, Groszmann RJ: Vasodilatation and sodium retention in prehepatic portal hypertension. Gastroenterology 1992; 102:931-935

55. La Villa G, Salmerón JM, Arroyo V, et al: Mineralocorticoid escape in patients with compensated cirrhosis and portal hypertension. Gastroenterology 1992; 102:2114-2119

56. Clària J, Jiménez W, Ros J, et al: Pathogenesis of arterial hypotension in cirrhotic rats with ascites: Role of endogenous nitric oxide. Hepatology 1992; 15:343-349

57. Gaeta GB, Perna P, Adinolfi LE, Utili R, Ruggiero G: Endotoxemia in a series of 104 patients with chronic liver diseases: Prevalence and significance. Digestion 1982; 23:239-244

58. Gray GA, Schott C, Julou-Schaeffer G, Fleming I, Parratt JR, Stoclet JC: The effect of inhibitors of the L-arginine/nitric oxide pathway on endotoxin-induced loss of vascular responsiveness in anaesthetized rats. Br J Pharmacol 1991; 103:1218-1224

59. Warren JB, Coughlan ML, Williams TJ: Endotoxin-induced vasodilatation in anaesthetized rat skin involves nitric oxide and prostaglandin synthesis. Br J Pharmacol 1992; 106:953-957

60. Hörtnagl H, Singer EA, Lenz K, Kleinberger G, Lochs H: Substance P is markedly increased in plasma of patients with hepatic coma. Lancet 1984; 1:480-483

61. Bruix J, Bosch J, Kravetz D, Mastai R, Rodés J: Effects of prostaglandin inhibition on systemic and hepatic hemodynamics in patients with cirrhosis of the liver. Gastroenterology 1985; 88:430-435

62. Benoit JN, Zimmerman B, Premen AJ, Go VL, Granger DN: Role of glucagon in splanchnic hyperemia of chronic portal hypertension. Am J Physiol 1986; 251:G674-G677

63. Villamediana LM, Sanz E, Fernandez-Gallardo S, et al: Effects of the platelet-activating factor antagonist BN 52021 on the hemodynamics of rats with experimental cirrhosis of the liver. Life Sci 1986; 39:201-205

64. Henriksen JH, Staun-Olsen P, Borg Mogensen N, Fahrenkrug J: Circulating endogenous vasoactive intestinal polypeptide (VIP) in patients with uraemia and liver cirrhosis. Eur J Clin Invest 1986; 16:211-216

65. Kravetz D, Arderiu M, Bosch J, et al: Hyperglucagonemia and hyperkinetic circulation after portacaval shunt in the rat. Am J Physiol 1987; 252:G257-G261

66. Caramelo C, Fernandez-Gallardo S, Santos JC, et al: Increased levels of platelet-activating factor in blood from patients with cirrhosis of the liver. Eur J Clin Invest 1987; 17:7-11

67. Schrier RW, Caramelo C: Hemodynamics and hormonal alterations in hepatic cirrhosis, *In* Epstein M (Ed): The Kidney in Liver Disease, 3rd edition. Baltimore, Md, Williams & Wilkins, 1988, pp 265-285

68. Silva G, Navasa M, Bosch J, et al: Hemodynamic effects of glucagon in portal hypertension. Hepatology 1990; 11:668-673

69. Bendtsen F, Schifter S, Henriksen JH: Increased circulating calcitonin gene-related peptide (CGRP) in cirrhosis. J Hepatol 1991; 12:118-123

70. Jespersen B, Jensen L, Sorensen SS, Pedersen EB: Atrial natriuretic factor, cyclic 3', 5'-guanosine monophosphate and prostaglandin E_2 in liver cirrhosis: Relation to blood volume and changes in blood volume after furosemide. Eur J Clin Invest 1990; 20:632-641

71. Laffi G, Pinzani M, Meacci E, et al: Renal hemodynamic and natriuretic effects of human atrial natriuretic factor infusion in cirrhosis with ascites. Gastroenterology 1989; 96:167-177

72. Koepke JP, Jones S, DiBona GF: Renal nerves mediate blunted natriuresis to atrial natriuretic peptide in cirrhotic rats. Am J Physiol 1987; 252:R1019-R1023

73. Sanz E, Caramelo C, López Novoa JM: Interstitial dynamics in rats with early stage experimental cirrhosis of the liver. Am J Physiol 1989; 256:F497-F503

74. Sanz E, López Novoa JM, Linares M, Digiuni E, Caramelo CA: Intravascular and interstitial fluid dynamics in rats treated with minoxidil. J Cardiovasc Pharmacol 1990; 15:485-492

75. Cosby RL, Yee B, Schrier RW: New classification with prognostic value in cirrhotic patients. Miner Electrolyte Metab 1989; 15:261-266

76. Davison JM: Kidney function in pregnant women. Am J Kidney Dis 1987; 9:248-252

77. Conrad KP, Morganelli PM, Brinck-Johnsen T, Colpoys MC: The renin-angiotensin system during pregnancy in chronically instrumented, conscious rats. Am J Obstet Gynecol 1989; 161:1065-1072

78. Baylis C, Reckelhoff JF: Renal hemodynamics in normal and hypertensive pregnancy: Lessons from micropuncture. Am J Kidney Dis 1991; 17:98-104

79. Durr JA, Stamoutsos B, Lindheimer MD: Osmoregulation during pregnancy in the rat—Evidence for resetting of the threshold for vasopressin secretion during gestation. J Clin Invest 1981; 68:337-346

80. Robertson GL: Thirst and vasopressin function in normal and disordered states of water balance. J Lab Clin Med 1983; 101:351-371

81. Niederberger M, Schrier RW: Evidence for a physiological role of nitric oxide (NO) in pregnancy (Abstr). J Am Soc Nephrol 1992; 3:549 [Abstr 18P]

82. Hayashi T, Fukuto JM, Ignarro LJ, Chaudhuri G: Basal release of nitric oxide from aortic rings is greater in female rabbits than in male rabbits: Implications for atherosclerosis. Proc Natl Acad Sci U S A 1992; 89:11259-11263

83. O'Connor KJ, Moncada S: Glucocorticoids inhibit the induction of nitric oxide synthase and the related cell damage in adenocarcinoma cells. Biochim Biophys Acta 1991; 1097:227-231

84. Conrad KP, Vernier KA: Plasma level, urinary excretion, and metabolic production of cGMP during gestation in rats. Am J Physiol 1989; 257:R847-R853

85. Conrad KP, Joffe GM, Kruszyna H, et al: Identification of increased nitric oxide biosynthesis during pregnancy in rats. FASEB J 1993; 7:566-571

86. Molnár M, Hertelendy F: Nw-nitro-L-arginine, an inhibitor of nitric oxide synthesis, increases blood pressure in rats and reverses the pregnancy-induced refractoriness to vasopressor agents. Am J Obstet Gynecol 1992; 166:1560-1567

87. Sarrel PM, Lindsay DC, Poole-Wilson PA, Collins P: Hypothesis: Inhibition of endothelium-derived relaxing factor by haemoglobin in the pathogenesis of pre-eclampsia. Lancet 1990; 336:1030-1032

88. Schrier RW, Briner VA: Peripheral arterial vasodilation hypothesis of sodium and water retention in pregnancy: Implications for pathogenesis of preeclampsia-eclampsia [see comments]. Obstet Gynecol 1991; 77:632-639