Hormonal alterations in liver disease: Implications for renal sodium retention

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INTRODUCTION

One of the most intriguing problems in clinical medicine is the «liver-kidney connection», i.e. the relationship between the diseased liver and the kidney that despite anatomic normality, often exhibits a wide spectrum of deranged function [1,2]. Prominent among such derangements is a progressive impairment of renal sodium handling, leading to the formation of ascites and edema, which frequently complicates the course of patients with decompensated Laennec's cirrhosis. This abnormality has been known for thousand of years [3,4]. Despite interest in and familiarity with this clinical entity, the managment of patients with liver disease and fluid retention has been largely empirical, consisting primarily of the administration of diuretics. The past several years have witnessed a resùrgence of interest in the investigation of deranged renal function in liver disease in general, and renal sodium handling in particular. A number of studies have succeeded in clarifying the mechanisms of the abnormal renal sodium handling. The available data have prompted a reappraisal of our thinking with regard to the pathophysiology of this abnormality and its management.

This chapter reviews the pathogenesis of the sodium retention of liver disease with an emphasis on the hormonal alterations that modulate this abnormality.

RENAL SODIUM HANDLING

Clinical features

Patients with Laennec's cirrhosis manifest a remarkable capacity for sodium chloride retention; indeed, they frequently excrete urine that is virtually free of sodium [5-7]. Extracellular fluid accumulates excessively and eventually becomes evident as clinically detectable ascites and edema. Cirrhotic patients who are unable to excrete sodium continue to gain weight and accumulate ascites and edema son long as dietary sodium content exceeds maximal urinary sodium excretion. If access to sodium is not curtailed, the relentless retention of sodium may lead to the accumulation of vast amounts of ascites (on occasion up to 22 liters). Weight gain and ascites formation cease when sodium intake is markedly limited.

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The abnormality of renal sodium handling in cirrhosis is not a static and unalterable condition. Rather, cirrhotic patients may undergo a spontaneous diuresis followed by a return to avid salt retention [7,8]. Although a considerable number of patients who are maintained on a sodium-restricted dietary program may demonstrate a spontaneous diuresis, there is inadequate information about the frequency with which this occurs. A report by Bosch et al [9] has suggested that a spontaneous diuresis occurs in one-third of patients with cirrhosis and ascites in response to bedrest and dietary sodium restriction. Patients who have *reversible* liver disease, such as those with alcohol-induced fatty liver, also tend to respond favorably when abstinent, rested, and fed a nutritious diet.

Although ascites is often viewed as an indicator of decompensated hepatic disease, this caveat does not always obtain. The onset of ascites can often be related directly to an increased dietary sodium intake and is more a reflection of salt loading than of progressive alterations in hepatic function with consequent renal changes. Occasionally a history of increased intake of salted foods in the period prior to entry to the hospital can be elicited, while other patients resort to the use of sodium-containing remedies such as antacids. If a history of recent increased sodium intake is elicited, spontaneous natriuresis often occurs when dietary sodium intake is restricted.

Finally, it cannot be overemphasized that the primary renal excretory abnormality causing fluid retention is a disturbance of sodium, rather than water excretion. Many sodium-retaining patients with ascites and edema can excrete urine of low osmolality when given excessive amounts of water without sodium [8,10,11]. Nevertheless, when sodium is administered, it is not excreted.

PATHOGENESIS

Despite extensive study, the mechanisms mediating the sodium retention of cirrhotic patients remain incompletely defined. Until rather recently focus has been on the importance of hyperaldosteronism, largely to the exclusion of other hormonal effectors. The past decade has witnessed a resurgence of interest in the reassessment of the putative predominance of hyperaldosteronsim in mediating this abnormality. Increased attention has been devoted to non-mineralocorticoid factors including alterations of renal prostaglandins and other vasoactive substances. The following section will review the reappraisal of our

thinking with regard to deranged renal sodium handling in the light of recent findings.

An examination of the pathogenetic events leading to the deranged sodium homeostasis of cirrhosis is simplified by a consideration of «afferent» events and «efferent» events. Since the afferent derangements that supervene in advanced liver disease have recently been reviewed in depth [12-14], I will only biefly review the concepts of a diminished effective volume and the «overflow» theory of ascites formation. The major emphasis will be placed on the efferent events mediating sodium retention.

In considering the «afferent» events, it would be worthwhile considering two concepts that have been frequently cited in any synthesis of the pathogenesis of the abnormal sodium retention of liver disease: a) the role of a diminished «effective» volume and b) the «overflow» theory of ascites formation.

A. AFFERENT EVENTS

1. Role of Diminished «Effective» Volume (i.e. «Underfill Theory»)

Traditionally, ascites formation in cirrhotic patients is considered to begin when a critical imbalance of Starling forces in the hepatic sinusoids and splanchnic capillaries causes an excessive amount of lymph formation, which exceeds the capacity of the thoracic duct to return it to the circulation [15,16]. Consequently, lymph accumulates in the peritoneal space as ascites, with a subsequent contraction of circulating plasma volume. Thus, as ascites develops, there is a progressive redistribution of plasma volume.

Although an imbalance of Starling forces in the hepatosplanchnic microcirculation is thought to be an important factor contributing to the relative decrease in effective blood volume, it should be emphasized that this is not the sole mechanism. An additional determinant is total peripheral resistance, which is diminished significantly in most edematous cirrhotic patients. Although total plasma volume may be increased in this setting the *effective* plasma volume (i.e. that part of total circulating volume that appears to stimulate volume receptors) is reduced. This diminution of effective volume is thought to constitute an afferent signal causing a secondary augmentation of renal sodium and water reabsorption. Thus, the traditional formulation suggests that the renal retention of sodium is a secondary rather than primary event.

This theory provides a possible explanation why fluid retention may fail to modify the stimulus for continuing sodium and water retention. Despite a progressive increase in total extracellular fluid volume, fluid is sequestered into one or more of the other fluid compartments without succeeding in normalizing effective blood volume. Only a correction of the disturbance in the forces governing fluid distribution will permit a reexpansion of effective blood volume to normal.

2. «Overflow Theory

Over the past decade, Lieberman and his associates have proposed an alternative hypothesis to the diminished effective volume theory: the «overflow» theory for ascites formation [17,18]. In contrast to the underfill formulation, the overflow theory postulates that the initial *primary* event is the inappropriate retention of excessive sodium by the kidneys. In the setting of abnormal Starling forces in the portal venous bed and hepatic sinusoids (both portal venous hypertension and a reduction in plasma colloid osmotic pressure), the expanded plasma volume is sequestered preferentially in the peritoneal space, with ascites formation. Thus, renal sodium retention and plasma volume expansion *precede rather than follow* the formation of ascites.

The promulgation of the overflow theory of ascites formation has engendered much controversy. The demonstration that plasma volume is increased in cirrhosis with ascites, and the finding that increases in measured plasma volume have not been observed in ascitic cirrhotic patients undergoing a spontaneous diuresis have been cited as evidence in support of the overflow hypothesis. Additional support derives from a series of elegant investigations carried out by Levy [19,20] on dogs with experimental portal cirrhosis demonstrating that renal sodium retention is the initial event that precedes ascites formation.

Althought these observations collectively support the overflow theory of ascites formation, a number of clinical observations in *man* are inconsistent with such a formulation. Thus, rapid volume expansion with exogenous solutions including saline, mannitol, and albumin frequently result in a transient improvement in renal sodium and water handling [21-23]. The results of many earlier studies must be considered inconclusive because of the confounding effects of the experimental designs.

Studies from our laboratory over the past 16 years have circumvented many of the experimental problems by applying a unique investigative tool, the water immersion model to the assessment of renal function and volume hormonal relationships [24-26]. Specifically, in contrast to saline administration, (a) water immersion is associated with a decrease in body weight, rather than the increase that attends saline infusion, (b) the «volume stimulus» of immersion is promptly reversible after cessation of immersion in contrast to the relatively sustained hypervolemia that follows saline administration and thus constitutes an important attribute in minimizing any risk to the patient, and (c) in contrast to saline administration, the «volume stimulus» of immersion occurs in the absence of changes in plasma composition [24-27].

Studies in 32 patients with decompensated cirrhosis demonstrated a striking «normalization» of renal sodium handling. As shown in Figure 1, immersion resulted in marked natriuresis and kaliuresis in the majority of these

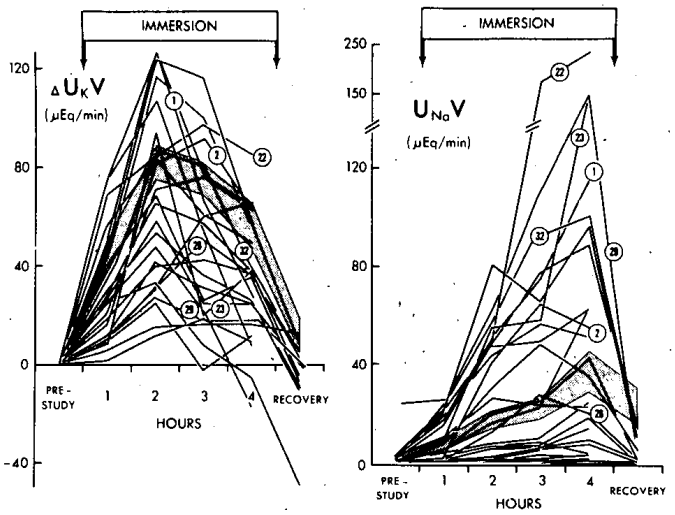

Fig. 1.—*Effects of water immersion following 1 hr of quiet sitting (prestudy) on rate of sodium excretion ($U_{Na}V$) and potassium excretion (U_KV) in a large group of patients with alcoholic liver disease. The circled numbers represent individual patients. Data for U_KV are expressed in terms of absolute changes from prestudy hour (ΔU_KV). The shaded area represents the mean ± SE for 14 normal control subjects undergoing an identical immersion study while ingesting an identical 10 meq sodium/100 meq potassium per day diet. Over half of the cirrhotic patients manifested an appropriate or «exaggerated» natriuretic response. In general, the increase in $U_{Na}V$ was associated with a concomitant increase in ΔU_KV.*

patients. During the final hour of immersion, $U_{Na}V$ was 20-fold greater than it was during the prestudy hour. Thus, the marked antinatriuresis of cirrhosis was promptly reversed by a manipulation that merely altered the distribution of plasma volume without increasing (and often decreasing) total plasma volume. Indeed in may instances the natriuresis of such patients exceeded markedly that manifested by normal subjects. Taken together, these studies lend strong support to the concept that a diminished *effective* intravascular volume is a major determinant of the enhanced tubular reabsorption of sodium in cirrhosis.

Although I believe that the presently available evidence favors a prominent role for diminished *effective* volume in mediating the avid sodium retention of many cirrhotic patients, it should be emphasized that these two formulations (i.e., diminished effective volume vs. overflow) may not be mutually exclusive. As noted above, cirrhosis is not a *static* disease, but rather a constantly evolving clinical disorder. Any formulation that suggests that the same antinatriuretic forces are operative throughout the evolution of sodium retention in cirrhotic man, is probably a marked oversimplification. Rather, one should adopt a more global view of the pathogenesis of abnormal sodium retention in cirrhosis in which differing forces participate in varying degrees as the derangement in sodium homeostasis evolves.

EFFERENT FACTORS

The initial attempts to explain the abnormalities of renal sodium handling focused on the decrement in glomerular filtration rate (GFR) that occurs frequently in patients with advanced liver disease. A number of observations indicate, however, that a decrease in GFR cannot constitute the major determinant of the abnormalities in renal sodium handling. Sodium retention occurs often despite preserved GFR. Furthermore, avid sodium reabsorption has been observed even in the face of supranormal GFR [8,29]. Thus the weight of evidence indicates that the renal sodium retention accompanying cirrhosis is attributable primarily to enhanced tubular reabsorption rather than to alterations in the filtered load of sodium. The precise nephron sites that are operative, however, remain the subject of continuing controversy [29,30,31].

The mediators of the enhanced tubular reabsorption of sodium in cirrhosis and their relative participation in the avid sodium retention have not been elucidated completely. Several hormonal, neural, and hemodynamic mechanism(s) have been suggested and are enumerated in Table 1. Those mechanism(s) for which there is some evidence, and their interrelationships are summarized schematically in Figure 2.

TABLE 1

MECHANISMS THAT HAVE BEEN SHOWN OR POSTULATED TO PARTICIPATE IN SODIUM RETENTION OF LIVER DISEASE

I.	**Changes in Hormonal Mediators**
	a. Hyperaldosteronism.
	b. Renal prostaglandins.
	c. Renal kallikrein-kinin system.
	d. Renin-angiotensin system.
	e. Natriuretic factor.
	f. Estrogens.
	g. Prolactin.
II.	**Neural and Hemodynamic**
	a. Alterations in intrarenal blood flow distribution.
	b. An increase in sympathetic nervous system activity.

Role of Hyperaldosteronism

Cirrhosis often is associated with increased levels of aldosterone in urine and plasma [27,32-34,36,37]. The elevation of plasma aldosterone is attributable to increased adrenal secretion and decreased metabolic degradation of the hormone. The rate of hepatic degradation is related directly to hepatic blood flow, which is markedly decreased in patients with decompensated cirrhosis.

Nevertheless, the etiologic relationship between hyperaldosteronism and sodium retention is uncertain. Initially, many observers seized on this observation and proposed that aldosterone is a major determinant of sodium retention [35]. In contrast to this long-held traditional view, many lines of evidence have challenged the etiologic role of elevated PA levels in mediating the sodium retention of cirrhosis: First, it should be noted that the widely held view that plasma aldosterone levels are usually elevated in advanced liver disease is probably an

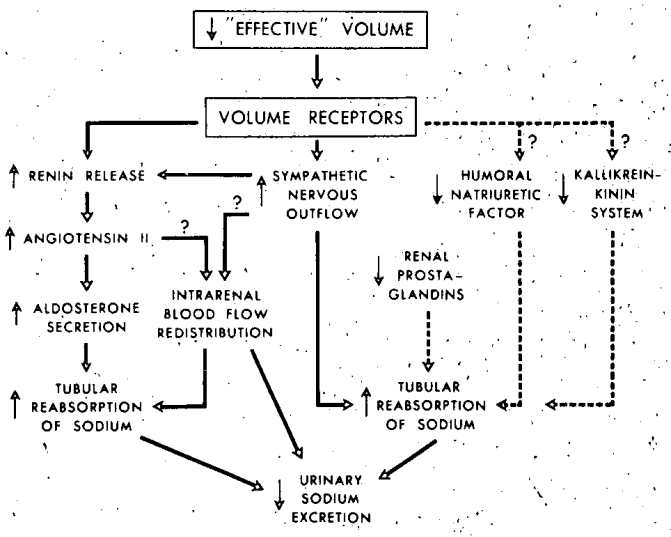

Fig. 2.—*Schematic drawing of possible mechanisms whereby a diminished* effective *volume results in sodium retention. The solid arrows indicate pathways for which evidence is available. The dashed lines represent proposed pathways, the existence of which remains to be established. (Reproduced with permission of the American Gastroenterological Association, Inc., from Epstein et al, Gastroenterology, 76:622-635, 1979).*

oversimplification [36] (Figure 3). Furthermore, increasing evidence demonstrates a dissociation between sodium excretion and plasma aldosterone in diverse clinical and experimental conditions, thereby challenging the predominance of elevated plasma aldosterone levels in mediating sodium retention in cirrhosis [34,36,37].

Immersion studies during chronic spironolactone administration permitted further elucidation of the relative contribution of aldosterone to sodium retention [38]. Spironolactone administration without immersion resulted in only a modest increase in sodium excretion. In contrast, there was a marked increase when immersion was performed during chronic spironolactone administration, thereby indicating that the major contribution to the natriuresis is enhanced distal delivery of filtrate [38]. More compelling evidence militating against a predominant role for aldosterone derives from recent immersion studies kinetically assessing the relationship of plasma aldosterone responsiveness to renal sodium handling [27]. Despite suppression in plasma aldosterone to comparable nadir levels in 16 cirrhotic patients, half the patients manifested absent or blunted natriuretic responses during immersion [27]. This demonstration of a dissociation between the suppression of circulating aldosterone and the absence of a natriuresis lends strong support to the interpretation that aldosterone is not the primary determinant of impaired sodium excretion in cirrhosis.

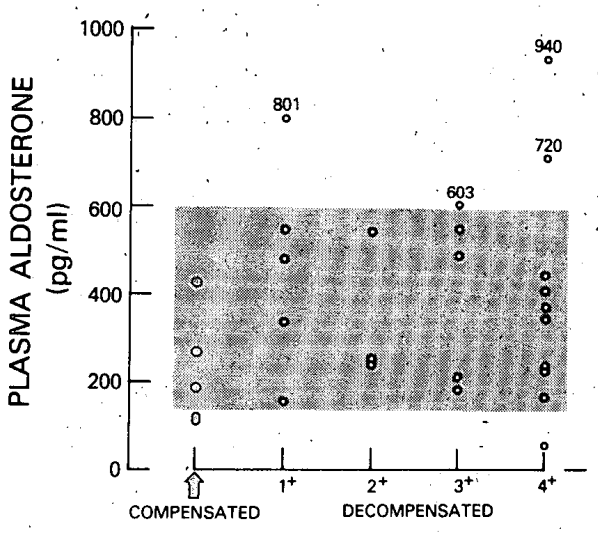

Fig. 3.—*An assessment of the relationship between plasma aldosterone (PA) levels and degree of ascites accumulation in 28 cirrhotic patients.* Closed circles *indicate compensated (absence of ascites and edema) patients.* Open circles *indicate patients with varying degrees of ascites and/or edema. The shaded area subtends the mean ± 2 SD for 14 normal subjects studied under identical conditions of sodium and potassium intake, posture, and time of day. As can be seen, relatively few patients manifested increments in PA despite advanced liver disease and ascites accumulation. (Reproduced with permission from M. Epstein, The Kidney in Liver Disease, Elsevier, 1983, page 385.)*

Role of Renal Prostaglandins and Renal Sodium Handling

The probability that prostaglandins participate in mediating the sodium retention of cirrhosis should be considered. Since several studies indicate that alterations in prostaglandin release may constitute a determinant of the natriuretic response to extracellular fluid volume expansion [39], it is probable that alterations in renal prostaglandin synthesis may contribute to derangements in renal sodium handling. Several studies have demonstrated that the administration of nonsteroidal antiinflammatory drugs (which act as inhibitors of prostaglandin synthetase) to patients with decompensated cirrhosis results in profound decrements of renal hemodynamics, GFR, and sodium excretion [40,41].

Since the above-cited studies have examined the effect of *inhibiting endogenous production* of renal prostaglandins, it was of great interest to assess an opposite experimental manipulation, i.e., augmentation of endogenous prostaglandins [42]. We utilized water immersion to the neck, which redistributes blood volume with concomitant central hypervolemia and *enhances PGE excretion* in normal man [39]. It was demonstrated that decompensated cirrhotic patients manifested an increase in mean PGE excretion that is three-fold greater than that observed in normal subjects studied under identical conditions [42]. This is attended by a marked *natriuresis* and an increase in creatinine clearance. Thus, when considered together, these studies indicate that derangements in renal PGE production appear to contribute to the renal dysfunction of cirrhosis, including sodium retention. It is tempting to postulate that in the setting of cirrhosis of the liver, enhancement of prostaglandin synthesis is a compensatory or adaptive response to incipient renal ischemia. It must be emphasized that these observations are not merely of academic interest, but have important clinical implications. They indicate that the administration of

NSAID agents that inhibit prostaglandin synthesis often results in clinically significant sodium retention and deterioriation of renal function. Since some NSAID agents are now readily accessible without a requirement for a physician's prescription, they constitute a major problem in the management of patients with advanced liver disease.

Role of Humoral Natriuretic Factor

Several lines of evidence suggest that a circulating natriuretic factor may constitute a component part of the biologic control system regulating sodium excretion in man [43-45]. It is conceivable, therefore, that deficiencies of this hormone could mediate, at least in part, sodium retention in cirrhosis (Fig. 3), i.e. that sodium retention results from a failure to elaborate natriuretic hormone when extracellular fluid volume increases in response to renal sodium retention.

Several preliminary observations utilizing bioassay systems are consistent with such a formulation [46-48]. Additional studies are needed to assess the precise role of a natriuretic factor in the pathogenesis of sodium retention in cirrhosis.

Sympathetic Nervous System Activity

An increase in sympathetic nervous system activity may also contribute to the sodium retention in cirrhosis [49]. Thus, the decrease in central blood volume could increase renal sympathetic activity [50,51]. Furthermore, recent studies have demonstrated that an increase in sympathetic tone promotes an antinatriuresis by altering intrarenal hemodynamics and by a direct tubular effect [50].

Although these theoretical considerations suggest a role for the sympathetic nervous system in the sodium retention of cirrhosis; relatively little data is available that bear directly on this possibility. Ring-Larsen et. al [52] reported elevated plasma norepinephrine levels in patients with advanced liver disease. Bichet et al. [53] have reported that patients with advanced cirrhosis manifest elevated concentrations of plasma catecholamines. These investigators proposed that the encountered catecholamine changes accounted for the impaired renal sodium and water handling in their patients.

Although most observers agree that mean peripheral norepinephrine levels are elevated in cirrhotic patients [52], it is an oversimplification to suggest that such alterations in catecholamine metabolism affect all cirrhotic patients with deranged sodium and water homeostasis. Recently, we have examined the relationship between plasma norepinephrine levels and renal sodium and water handling during immersion-induced central blood volume expansion [54]. Although mean norepinephrine levels were elevated for the group as a whole, more than half of the patients with decompensated cirrhosis manifested appropriate (unelevated) norepinephrine levels. Furthermore, norepinephrine levels did not correlate with alterations in renal sodium or water excretion [54] (Figures 4 & 5).

The available data regarding the role of the sympathetic nervous system may be summarized as fragmentary and inconclusive. More direct indices of autonomic activity (such as renal venous norepinephrine levels rather than peripheral plasma levels) are required to determine whether diminished effective volume with a concomitant increase in sympathetic activity, both in the kidney and in other areas, contributes to the sodium retention of cirrhosis [55].

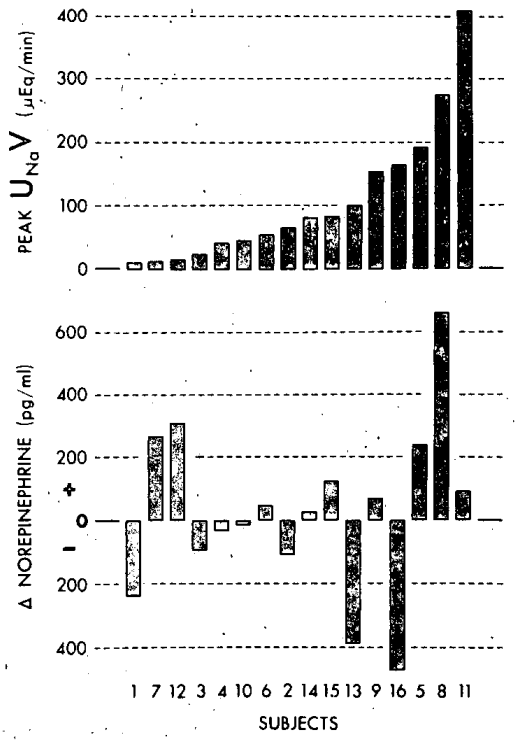

Fig. 4.—*Relationship of renal sodium excretion (upper panel) to alterations in plasma NE (lower panel) during immersion in sixteen cirrhotic patients. The numbers along the horizontal axis designate the individual patients. As can be seen, the magnitude of the natriuresis, as assessed by peak $U_{Na}V$ varied independently of ΔNE («nadir» minus prestudy NE) during immersion (r = 0.256; N.S.) (reproduced with permission from M. Epstein et al, ref. 54).*

Kallikrein-Kinin System

The possibility that the kallikrein-kinin system may contribute to the mediation of sodium retention of liver disease is raised by several preliminary reports of abnormalities of the plasma kallikrein system [56,57]. Since bradykinin has been suggested to be a physiologic renal vasodilator, it is possible that failure of bradykinin formation may contribute to the renal cortical vasoconstriction documented in patients with decompensated cirrhosis. The data so far are sparse but provocative.

Role of Atrial Natriuretic Factor (Auriculin)

It has been recently shown that mammalian atria

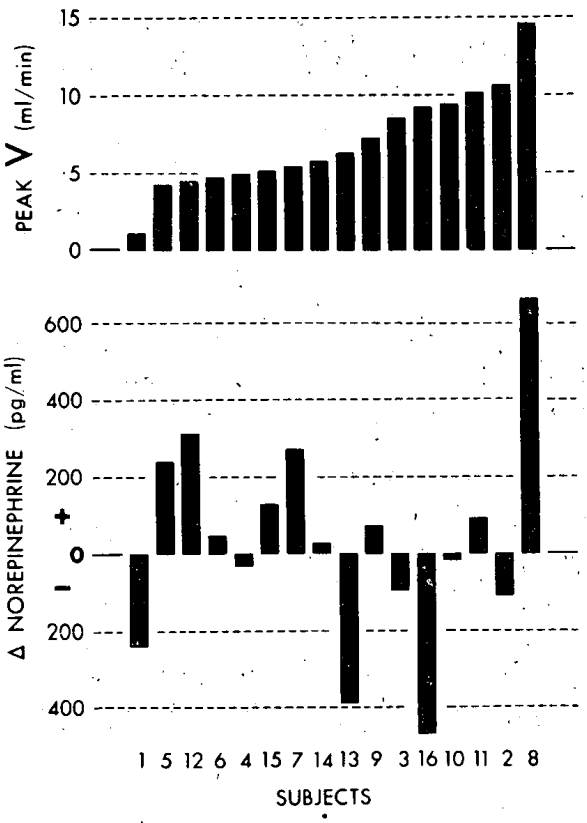

Fig. 5.—*Relationship of renal water handling (upper panel) to alterations in plasma NE (lower panel) during immersion in sixteen cirrhotic patients. The numbers along the horizontal axis designate the individual patients. As can be seen, the magnitude of the diuresis, as assessed by peak V, varied independently of ΔNE («nadir» minus prestudy NE) during immersion (r = 0.239; N.S.) (reproduced with permission from M. Epstein et al, ref. 54.)*

contain potent natriuretic and vasoactive peptide(s) that have been referred to as atrial natriuretic factor and auriculin [58]. Several laboratories have purified, sequenced, and synthesized atrial peptides that have the natriuretic and vasoactive properties of crude atrial extract. Studies in intact animals have demonstrated that ANF decreases blood pressure and increases glomerular filtration rate and sodium excretion without a sustained increase in renal plasma flow. In addition, synthetic auriculin decreased renin secretory rate, plasma renin levels, and plasma aldosterone levels [59]. Taken together, these observations suggest an important potential role for ANF in the regulation of blood pressure, renal function, and sodium-volume homeostasis.

In light of several lines of evidence suggesting that stretch receptors residing in the atria may participate in regulating volume homeostasis [60], it is tempting to attribute a cardinal role to this peptide in modulating renal sodium handling in both normal man and edematous disorders including chronic liver disease. Specifically, both the sodium retention and the activation of the renin-angiotensin-aldosterone system in patients with cirrhosis may result from a failure to elaborate ANF when ECF volume increases in response to renal sodium retention. In light of active investigations in many laboratories with these peptides, it is hoped that the role for this putative effector in mediating sodium retention in cirrhotic man will be delineated.

The above six sections exemplify the mechanisms which may contribute to the deranged sodium homeostasis of cirrhosis. It is apparent that the renal sodium retention of advanced liver disease is a complex pathophysiologic constellation with numerous and diverse causes. Figure 2 represents an attempt to integrate these diverse findings and to summarize some of the mechanisms whereby these diverse hormonal mediators may act in concert to induce sodium retention. Additional studies are necessary to further define the interrelationship of these hormonal mediators in mediating the derangements of renal sodium handling. Such observations will provide a rational basis for the clinical management of the disorder.

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