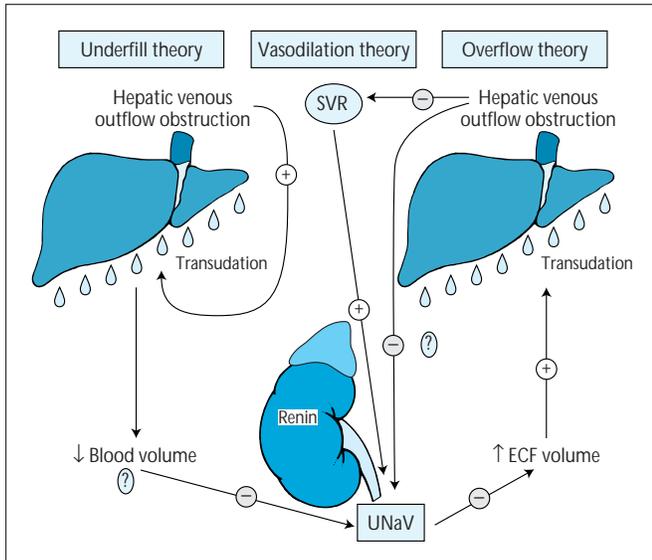
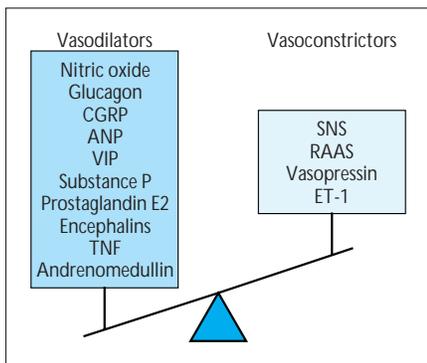


## Mechanisms of Extracellular Fluid Volume Expansion in Cirrhosis



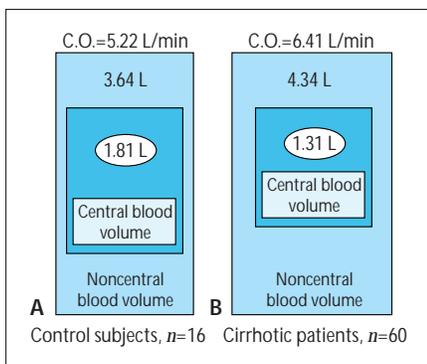
**FIGURE 2-30**

Three theories of ascites formation in hepatic cirrhosis. Hepatic venous outflow obstruction leads to portal hypertension. According to the *underfill theory*, transudation from the liver leads to reduction of the blood volume, thereby stimulating sodium (Na) retention by the kidney. As indicated by the question mark near the term *blood volume*, a low blood volume is rarely detected in clinical or experimental cirrhosis. Furthermore, this theory predicts that ascites would develop before renal Na retention, when the reverse generally occurs. According to the *overflow theory*, increased portal pressure stimulates renal Na retention through incompletely defined mechanisms. As indicated by the question mark near the arrow from hepatic venous outflow obstruction to  $U_{Na}V$ , the nature of the portal hypertension-induced signals for renal Na retention remains unclear. The *vasodilation theory* suggests that portal hypertension leads to vasodilation and relative arterial hypotension. Evidence for vasodilation in cirrhosis that precedes renal Na retention is now convincing, as shown in Figures 2-31 and 2-33 [63].



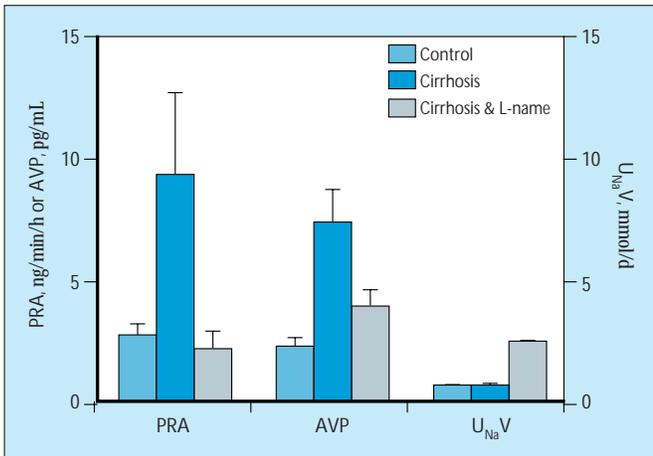
**FIGURE 2-31**

Alterations in cardiovascular hemodynamics in hepatic cirrhosis. Hepatic dysfunction and portal hypertension increase the production and impair the metabolism of several vasoactive substances. The overall balance of vasoconstriction and vasodilation shifts in favor of dilation. Vasodilation may also shift blood away from the central circulation toward the periphery and away from the kidneys. Some of the vasoactive substances postulated to participate in the hemodynamic disturbances of cirrhosis include those shown here. ANP—atrial natriuretic peptide; ET-1—endothelin-1; CGRP—calcitonin gene related peptide; RAAS—renin/angiotensin/aldosterone system; TNF—tumor necrosis factor; VIP—vasoactive intestinal peptide. (Data from Møller and Henriksen [64].)

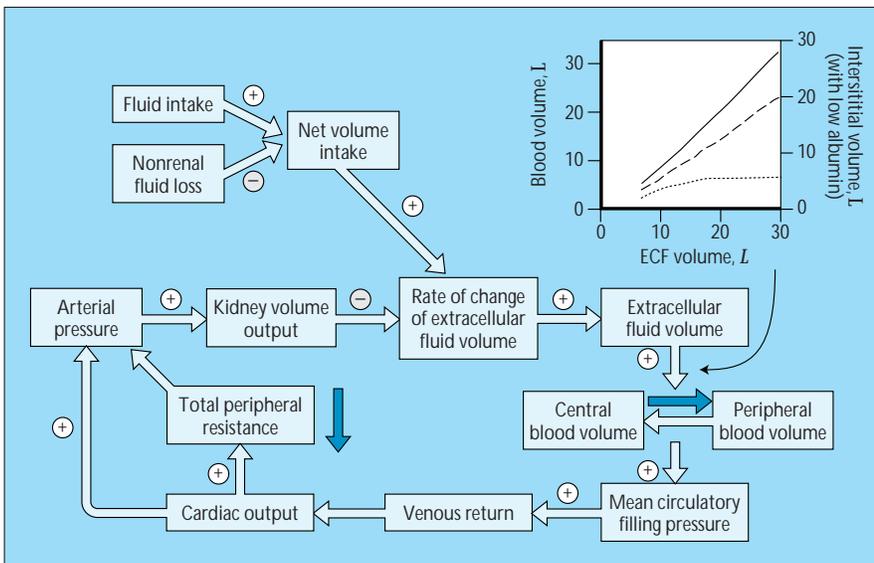


**FIGURE 2-32**

Effects of cirrhosis on central and noncentral blood volumes. The central blood volume is defined as the blood volume in the heart, lungs, and central arterial tree. Compared with control subjects (A), patients with cirrhosis (B) have decreased central and increased noncentral blood volumes. The higher cardiac output (CO) results from peripheral vasodilation. Perfusion of the kidney is reduced significantly in patients with cirrhosis. (Data from Hillarp and coworkers [65].)

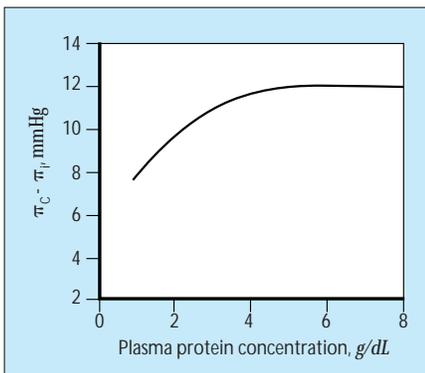


**FIGURE 2-33** Contribution of nitric oxide to vasodilation and sodium (Na) retention in cirrhosis. Compared with control rats, rats having cirrhosis induced by carbon tetrachloride and phenobarbital exhibited increased plasma renin activity (PRA) and plasma arginine vasopressin (AVP) concentrations. At steady state, the urinary Na excretion ( $U_{Na}V$ ) was similar in both groups. After treatment with L-NAME for 7 days, plasma renin activity decreased to normal levels, AVP concentrations decreased toward normal levels, and urinary Na excretion increased by threefold. These changes were associated with a normalization of mean arterial pressure and cardiac output. (Data compiled from Niederberger and coworkers [66,67] and Martin and Schrier [68].)



**FIGURE 2-34** Mechanisms of sodium (Na) retention in cirrhosis. A primary decrease in systemic vascular resistance (indicated by dark blue arrow), induced by mediators shown in Figure 2-31, leads to a decrease in arterial pressure. The reduction in systemic vascular resistance, however, is not uniform and favors movement of blood from the central (“effective”) circulation into the peripheral circulation, as shown in Figure 2-32. Hypoalbuminemia shifts the interstitial to blood volume ratio upward (compare the interstitial volume with normal [*dashed line*], and low [*solid line*], protein levels in the inset graph). Because cardiac output increases and venous return must equal cardiac output, dramatic expansion of the extracellular fluid (ECF) volume occurs.

## Mechanisms of Extracellular Fluid Volume Expansion in Nephrotic Syndrome



**FIGURE 2-35** Changes in plasma protein concentration affect the net oncotic pressure difference across capillaries ( $\pi_c - \pi_i$ ) in humans. Note that moderate reductions in plasma protein concentration have little effect on differences in transcapillary oncotic pressure. Only when plasma protein concentration decreases below 5 g/dL do changes become significant. (Data from Fadnes and coworkers [69].)

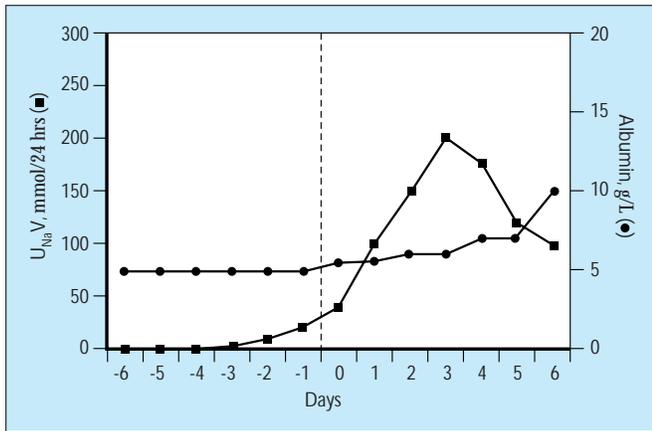


FIGURE 2-36

Time course of recovery from minimal change nephrotic syndrome in five children. Note that urinary Na excretion (squares) increases before serum albumin concentration increases. The data suggest that the natriuresis reflects a change in intrinsic renal Na retention. The data also emphasize that factors other than hypoalbuminemia must contribute to the Na retention that occurs in nephrosis.  $U_{Na}V$ —urinary Na excretion volume. (Data from Oliver and Owings [70].)

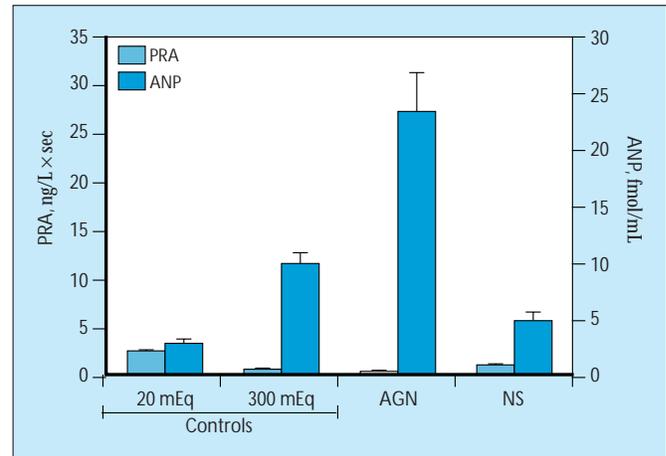


FIGURE 2-37

Plasma renin activity (PRA) and atrial natriuretic peptide (ANP) concentration in the nephrotic syndrome. Shown are PRA and ANP concentration (+standard error) in normal persons ingesting diets high (300 mEq/d) and low (20 mEq/d) in sodium (Na) and in patients with acute glomerulonephritis (AGN), predominantly post-streptococcal, or nephrotic syndrome (NS). Note that PRA is suppressed in patients with AGN to levels below those in normal persons on diets high in Na. PRA suppression suggests that primary renal NaCl retention plays an important role in the pathogenesis of volume expansion in AGN. Although plasma renin activity in nephrotic syndrome is not suppressed to the same degree, the absence of PRA elevation in these patients suggests that primary renal Na retention plays a significant role in the pathogenesis of Na retention in NS as well. (Data from Rodriguez-Iturbe and coworkers [71].)

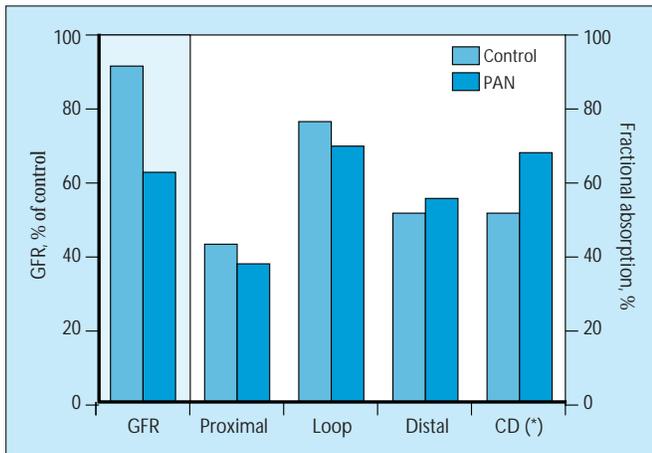


FIGURE 2-38

Sites of sodium (Na) reabsorption along the nephron in control and nephrotic rats (induced by puromycin aminonucleoside [PAN]). The glomerular filtration rates (GFR) in normal and nephrotic rats are shown by the hatched bars. Note the modest reduction in GFR in the nephrotic group, a finding that is common in human nephrosis. Fractional reabsorption rates along the proximal tubule, the loop of Henle, and the superficial distal tubule are indicated. The fractional reabsorption along the collecting duct (CD) is estimated from the difference between the end distal and urine deliveries. The data suggest that the predominant site of increased reabsorption is the collecting duct. Because superficial and deep nephrons may differ in reabsorptive rates, these data would also be consistent with enhanced reabsorption by deep nephrons. Asterisk—data inferred from the difference between distal and urine samples. (Data from Ichikawa and coworkers [72].)