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Salt Sensitivity in Hypertension
Renal and Cardiovascular Implications

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Abstract The mechanisms responsible for the increase in blood pressure response to high salt intake in salt-sensitive patients with essential hypertension are complex and only partially understood. A complex interaction between neuroendocrine factors and the kidney may underlie the propensity for such patients to retain salt and develop salt-dependent hypertension. The possible role of vasodilator and natriuretic agents, such as the prostaglandins, endothelin-1, and kinin-kallikrein system, requires further investigation. An association between salt sensitivity and a greater propensity to develop renal failure has been described in certain groups of hypertensive patients, such as blacks, the elderly, and those with diabetes mellitus. Salt-sensitive patients with essential hypertension manifest a deranged renal hemodynamic adaptation to a high dietary salt intake. During a low salt diet, salt-sensitive and salt-resistant patients have similar mean arterial pressure, glomerular filtration rate, effective renal plasma flow, and filtration fraction. On the other hand, during a high salt intake glomerular filtration rate does not change in either group, and effective renal blood flow increases in salt-resistant but decreases in salt-sensitive patients; filtration fraction and glomerular capillary pressure decrease in salt-resistant but increase in salt-sensitive patients. Salt-sensitive patients are also more likely than salt-resistant patients to manifest left ventricular hypertrophy, microalbuminuria, and metabolic abnormalities that may predispose them to cardiovascular diseases. In conclusion, salt sensitivity in hypertension is associated with substantial renal, hemodynamic, and metabolic abnormalities that may enhance the risk of cardiovascular and renal morbidity.

Key Words • hypertension, sodium-dependent • sodium • norepinephrine • renal circulation • natriuresis • microalbuminuria

Despite extensive research, controversy still exists regarding the role of dietary salt (NaCl) in hypertension. Epidemiologic studies have demonstrated a significant but weak relation between salt intake and hypertension. Some intervention studies have shown that salt restriction may lower blood pressure. Some researchers dispute the importance of this issue on the grounds that the effects of salt restriction on blood pressure are unpredictable and on the average modest and difficult to determine; also, compliance with a salt-restricted diet is not easily achieved. Some even point to potential detrimental neurohumoral and metabolic effects of an indiscriminate dietary NaCl restriction. However, these effects appear to be transient and evident only when an extreme dietary Na^+ restriction of 10 to 20 mEq/d is applied. In addition, the metabolic abnormalities caused by salt restriction are self-correcting, despite continuing low salt intake, and appear to be mediated by increased sympathetic nerve activity, because they can be prevented by α1-adrenergic blocking agents.

Watt has recently raised several concerns with regard to the concept of salt sensitivity, the methods used for its definition, and its clinical significance. Although not denying its biologic basis, Watt argues that there is little direct scientific evidence for salt sensitivity in hypertension, that the effect of sodium restriction on blood pressure is related to the severity of hypertension, and that the potential usefulness of definitions of salt sensitivity is questionable because there is no quick and inexpensive test that can be applied to large numbers of patients. Notwithstanding these arguments, the validity of the concept and need for further studies in the field are supported by the evidence (admittedly largely indirect) that salt sensitivity is more prevalent in certain ethnic groups, is independent of the severity of hypertension, and is not a random phenomenon because it is reproducible, when defined according to rigorous protocols. Watt's argument against the usefulness of this definition because it cannot be determined quickly and affordably remains valid but only until such tests are developed. Attempts to characterize salt sensitivity on the basis of simple biochemical analysis are currently underway, with encouraging results.

Metabolic balanced studies offer the best opportunity for studying the effects of different salt intakes on blood pressure and the mechanisms responsible for those effects. The major limitation of these studies is that they can be performed in only a restricted number of subjects. Kawasaki et al described a variable effect of high NaCl intake on blood pressure in human subjects and classified patients with essential hypertension as salt sensitive or not salt sensitive based on their blood pressure response to an NaCl load. Several other laboratories have confirmed the variable effect of dietary NaCl on blood pressure. Weinberger et al studied the blood pressure response to rapid volume expansion and contraction in...
192 hypertensive patients and more than 300 healthy subjects. They classified 51% of patients with hypertension as salt sensitive, 16% as salt resistant, and the remaining as having an intermediate response. We have classified as salt sensitive those patients who manifest a rise in blood pressure of at least 10 mm Hg during a 200 mEq/d Na+ diet compared with a diet containing only 10 to 20 mEq/d Na+ and found approximately 50% of patients with essential hypertension to be salt sensitive.15 In some of the salt-sensitive patients the difference in mean arterial pressure between the low and high NaCl intake was 37 mm Hg, a difference that one can hardly consider insignificant and unworthy of further study. Several studies have also shown that salt sensitivity defined according to these rigid protocols is highly reproducible even in normotensive subjects.22,23 This observation speaks against the possibility of a random effect of NaCl intake on blood pressure.

The blood pressure changes in response to a high NaCl intake follow a gaussian distribution.16 Thus, salt-sensitive individuals do not represent a discrete, well-defined subset of patients, and any subdivision of hypertensive patients according to this criterion is arbitrary. Nonetheless, substantial hemodynamic and hormonal differences have been identified between these two subgroups to justify this subdivision and continued investigation of the subject.

We believe that the concept of salt sensitivity is biologically sound and that, from the public health point of view, the primary focus of attention concerning salt sensitivity should not be whether the phenomenon exists or whether salt sensitivity is based on genetic or acquired factors but rather what the effect of high salt intake is, not only on blood pressure but also and foremost on cardiovascular morbidity and mortality.

The main purpose of this article is not to review the epidemiologic evidence supporting the concept of salt sensitivity or the arguments for and against the validity of the concept, a task recently performed by others.2 Rather, we will review the mechanisms that may underlie salt sensitivity and, more importantly, the evidence that salt sensitivity may have adverse effects or be associated with a greater incidence of cardiovascular and renal complications.

Demographic Characteristics of Salt-Sensitive Patients

The prevalence of salt sensitivity appears to be greater in blacks and older patients than in whites or younger hypertensive patients.24 It also appears to be more frequent among obese patients or those with concomitant diabetes mellitus.25,26

What Causes Salt Sensitivity?

Sodium-Retention and Hemodynamic Characteristics

Guyton et al27 were among the first to point to a primacy of the kidney in the genesis or maintenance of hypertension and to suggest that hypertension may be a necessary consequence of the reduced ability of the kidney to excrete a salt load to promote natriuresis and maintain a normal sodium balance.

One frequent finding among salt-sensitive patients with essential hypertension is an increase in sodium retention during a high NaCl diet.14,26,29 Other studies, however, have not been able to demonstrate differences in sodium balance between salt-sensitive and salt-resistant patients.13 Others have shown a longer half-life of sodium balance in salt-sensitive compared with salt-resistant patients despite no difference in salt retention.30 Most studies have also been unable to show a statistically significant relation between the amount of sodium lost during depletion or retained during NaCl loading and changes in arterial pressure.1

The slope of the renal function (pressure-natriuresis) curve is significantly lower in salt-sensitive than salt-resistant patients (Fig 1),21,31 suggesting a disturbance in renal tubular sodium reabsorption.

According to Guyton's concept, sodium retention and the consequent volume expansion initially increase cardiac output. Subsequently, because of a process of local autoregulation, peripheral vascular resistance progressively rises so that the chronic elevation of NaCl-related hypertension is maintained by an increase in peripheral vascular resistance rather than in cardiac output. This sequence of events is difficult to ascertain in human subjects, because the time of initiation of hypertension frequently is not determined. Fujita et al20 studied the effects of a low and high NaCl diet, each given for 1 week, on cardiac output and peripheral vascular resistance in seven salt-sensitive and seven non–salt-sensitive patients. The increment of cardiac output between the low- and high-sodium diets was significantly greater in salt-sensitive than non–salt-sensitive patients, whereas total peripheral resistance did not change significantly in either group. A significant positive correlation was observed between the increment in cardiac output and the increment in mean blood pressure. These studies would be in keeping with Guyton's hypothesis that, at least acutely, the NaCl-related hypertension is due to an increase in cardiac output. Unfortunately, the studies were not continued for a sufficient length of time to verify whether with time cardiac output normalized and hypertension was maintained by a rise in total peripheral resistance.

Sullivan et al32 measured cardiac index, total peripheral resistance, and forearm blood flow in 58 normotensive subjects and 51 patients with borderline hypertension and observed that salt-sensitive subjects had significantly higher forearm vascular resistance, lower forearm blood flow, and lower conjunctival capillary density, whereas cardiac index was similar between the two groups during both a low and high NaCl intake.
Mark et al. found decreased forearm blood flow during NaCl loading in patients with borderline hypertension, suggesting vasoconstriction. In this study, however, patients were not classified according to salt sensitivity.

In elderly patients with hypertension, Shimamoto and Shimamoto showed that the hemodynamic response to an NaCl load changed with time. Initially, the rise in blood pressure was sustained by an increase in cardiac output; but by the end of 2 weeks, hypertension in most patients was sustained by a rise in peripheral vascular resistance. In some patients, the increment in blood pressure was sustained by a rise in cardiac index even after 3 weeks of a high NaCl intake. The patients whose blood pressure elevation in response to an NaCl load was primarily due to a rise in cardiac index manifested a predominant rise in systolic blood pressure, whereas those patients with increased peripheral vascular resistance manifested a predominant rise in diastolic blood pressure.

The sequence of hemodynamic responses to a high dietary intake of NaCl is easier to determine in experimental animals. Ganguli et al. measured cardiac output and peripheral vascular resistance during high and low NaCl intakes in Dahl salt-sensitive (DS) and Dahl salt-resistant (DR) rats. During low NaCl intake, cardiac output and peripheral vascular resistance were similar between the two rat strains. During high NaCl intake, however, cardiac output increased equally in the two strains; peripheral vascular resistance decreased in DR but increased in DS rats. Simchon et al. confirmed that after 4 weeks of an 8% NaCl diet, hypertension in DS rats was sustained by an increase in blood volume and cardiac output; after 8 weeks, cardiac output decreased to levels below normal, and hypertension was sustained by an increase in total peripheral resistance. After 46 weeks of a 1% NaCl diet, blood pressure increased significantly in the DS rats because of a rise in total peripheral resistance, whereas cardiac output decreased compared with controls.

Taken together, these studies support Guyton’s notion that the hemodynamic response to NaCl loading varies with time and that chronically, the NaCl-related rise in blood pressure is sustained primarily by a rise in peripheral vascular resistance.

Abnormal Renal Hemodynamics

Substantial differences in renal hemodynamic adaptation to a high dietary sodium intake are evident between salt-sensitive and salt-resistant patients. During a high NaCl intake, glomerular filtration rate did not change, renal blood flow increased, and renal vascular resistance and filtration fraction decreased in salt-resistant patients, a hemodynamic response similar to that of normotensive subjects. In salt-sensitive patients, however, high NaCl intake caused no change in glomerular filtration rate, a decrease in renal blood flow, and an increase in renal vascular resistance, suggesting a parallel rise in intraglomerular pressure. Calculation of intraglomerular pressure using the Gomez formula confirmed that a high NaCl diet increased intraglomerular pressure in salt-sensitive patients but decreased intraglomerular pressure in salt-resistant patients (Fig 2). Although results obtained with these formulas must be regarded as approximations and interpreted with caution, it is of interest that they substantiate the differences in filtration fraction between salt-sensitive and salt-resistant patients in response to a high dietary NaCl intake.

Before our study, in a group of patients with essential hypertension and normal or high plasma renin activity (PRA), Williams and Hollenberg observed a defect in the modulation of renal blood flow and aldosterone response to angiotensin II (Ang II) with changes in dietary NaCl intake. In these patients, defined as non-modulators, renal blood flow failed to increase in response to a high NaCl intake, whereas in normotensive subjects and hypertensive patients with normal renal vascular and adrenal modulation, renal blood flow increased by at least 120 mL/min per 1.73 m².

These hemodynamic and hormonal derangements could be reversed by the administration of an angiotensin-converting enzyme inhibitor. Non-modulators also manifested a derangement in the renal capacity to handle sodium; the half-time of the exponential function relating sodium excretion to time was prolonged in non-modulating patients. Evidence also suggests that non-modulation may be inherited.

Many of the renal hemodynamic characteristics observed in the non-modulators mimic those we observed in salt-sensitive patients. The difference between these two studies is that we did not select patients with normal PRA, a criterion that would have excluded most of the hypertensive blacks, who have notoriously reduced PRA levels. In addition, in the study by Williams and Hollenberg, patients were not selected on the basis of their blood pressure sensitivity to NaCl intake but rather on the basis of renal hemodynamic and hormonal responses to different NaCl diets. In their patients, when balance was achieved with a sodium
intake of 10 mEq, the fall in blood pressure was similar in modulators and non-modulators. Conversely, during the shift in sodium intake from 10 to 200 mEq/d, an increase in blood pressure of 10 mm Hg or greater was observed in 12 of the 19 non-modulating patients but in none of the 17 modulating patients. These studies indicate that not all the so-called non-modulators are salt sensitive and that the two terms cannot be used interchangeably.

Other investigators have measured renal hemodynamics in black hypertensive patients, but most of them did not take into account the potential effect of different NaCl intakes. Levy et al\(^{43}\) showed a significant reduction in renal blood flow and a failure of urinary kallikrein to increase in response to sodium depletion in black hypertensive patients. They also observed that black hypertensive patients manifested more severe angiographic signs of nephrosclerosis than white patients. Frohlich et al\(^{44,45}\) measured cardiac output, plasma volume, and renal blood flow in blacks and whites matched for sex, age, and arterial pressure and found no differences in cardiac output, vascular resistance, plasma volume, and total blood volume but a significantly lower renal blood flow and higher renal vascular resistance in blacks than whites. Lowenstein et al\(^{46}\) used direct measurements of wedged renal vein pressure to calculate renal interstitial pressure and glomerular capillary pressure and found an increase in glomerular capillary pressure in patients with essential hypertension despite an increase in renal afferent resistance. In that study, however, dietary NaCl intake and the race of the patients were not considered.

In conclusion, the link between renal hemodynamic abnormalities and salt sensitivity in hypertension is unclear. It is possible that renal hemodynamic derangements are responsible for Na\(^+\) retention, but a cause-effect relation has not been clearly established.

**Role of the Sympathetic Nervous System**

Extensive evidence suggests that sodium retention and hypertension in salt-sensitive subjects may be dependent on increased activity of the sympathetic nervous system or an increase in the ratio of norepinephrine to dopamine secretion.\(^{47}\) Several years ago we showed that salt-sensitive patients with essential hypertension displayed an abnormal relation between urinary sodium excretion and plasma norepinephrine levels.\(^{48}\) A high NaCl diet was accompanied by a decrease in plasma concentrations of norepinephrine in normotensive subjects\(^{49}\) and salt-resistant patients but not in salt-sensitive patients.\(^{50}\) This finding has been confirmed by several other investigators.\(^{51,52}\) Dietary NaCl loading in borderline hypertensive patients produced greater decreases in renal blood flow, enhanced renal vasoconstriction, and enhanced water retention during standing, suggesting an abnormality in the neurohumoral control of the renal circulation.\(^{53}\)

A high NaCl diet has also been shown to stimulate rather than suppress sympathetic nervous system activity in spontaneously hypertensive rats (SHR) and DS rats.\(^{54-58}\) Renal denervation promotes natriuresis and delays the development of hypertension in SHR.\(^{59}\) Stimulation of renal sympathetic outflow may alter renal function and the normal relation between arterial pressure and natriuresis and diuresis.\(^{60}\) Thus, an increase in renal sympathetic nerve activity could shift the pressure-natriuresis relation toward higher pressure and be responsible for the sodium retention.\(^{61-64}\)

More recently, we observed that the blood levels of norepinephrine achieved during the infusion of fixed amounts of this hormone were lower in salt-sensitive than salt-resistant patients, suggesting substantial differences in norepinephrine metabolism between these two groups.\(^{2}\)

Trimarco et al\(^{65}\) have shown that a high NaCl diet sensitizes cardiopulmonary baroreceptor reflexes in salt-resistant but not salt-sensitive hypertensive patients and have suggested that the lack of compensatory augmentation in cardiopulmonary baroreceptor reflex function may contribute to salt sensitivity. Similarly, a high NaCl diet sensitized the cardiopulmonary baroreceptor reflex modulation of sympathetic nerve activity in DR but not DS rats.\(^{66}\)

There is considerable evidence that dopamine has potent natriuretic and vasoactive properties. Urinary dopamine excretion increases during dietary salt loading.\(^{67}\) Administration of dopamine causes natriuresis,\(^{68,69}\) and the natriuresis associated with acute volume expansion can be attenuated by dopamine receptor antagonists.\(^{70}\) These studies have led to the commonly accepted notion that renal dopamine participates in the homeostatic regulation of NaCl balance.\(^{71,72}\) Low doses of dopamine increase renal blood flow and urinary excretion of prostacyclin (prostaglandin I\(_2\) [PGI\(_2\)]) in normotensive subjects.\(^{73}\) Thus, a decrease in renal dopamine production could decrease both renal blood flow and urinary Na\(^+\) excretion. Locally produced dopamine causes a reversible and dose-dependent inhibition of Na\(^+\),K\(^+\)-ATPase activity in rat proximal tubule segments, and this inhibitory effect is enhanced by a high NaCl intake.\(^{74}\)

Dopamine and norepinephrine exert opposite effects on renal Na\(^+\) handling, so that an increase in the ratio of norepinephrine to dopamine could result in Na\(^+\) retention. Gill et al\(^{75}\) have shown a decrease in dopamine and increase in norepinephrine excretion in salt-sensitive patients, suggesting that a reduction in dopamine secretion may contribute to salt sensitivity and hypertension in these patients. These investigators have also observed that salt-sensitive patients have an exaggerated response of urinary dopa excretion to salt loading, and they have suggested that a low ratio of dopamine to dopa in urine may be used as a marker for salt sensitivity.\(^{75}\) Similar findings have been observed in hypertensive rats. After injection of tyrosine, DS rats have a higher adrenal synthesis of norepinephrine, a higher adrenal norepinephrine and epinephrine content, but a lower dopamine content in the kidney and heart and lower urinary excretion of dopamine than DR rats.\(^{76}\) This suggests that during high NaCl intake, DS rats may be unable to turn off the increase in adrenal norepinephrine synthesis from dopamine.

Abnormalities in dopaminergic control of blood pressure have been shown by other investigators.\(^{77,78}\) In 22 hypertensive patients, Hamasaki et al\(^{79}\) evaluated central dopaminergic activity by measuring the plasma prolactin response to intravenous thyrotropin-releasing hormone and found a lower prolactin response in salt-sensitive patients and a negative correlation be-
between the percentage change of prolactin and the change in blood pressure in response to an NaCl load.

Bugli et al have shown that dopamine and fenoldopam, a dopamine type 1 agonist, do not increase renal blood flow or PGI2 in patients with essential hypertension, suggesting an alteration in dopaminergic tone characterized by a defect in dopamine receptor sensitivity; however, these authors did not examine potential differences in the responses between salt-sensitive and salt-resistant patients.

In all, the evidence supports a role for the sympathetic nervous system in the genesis of NaCl-related hypertension and renal hemodynamic derangements in salt-sensitive patients.

**Increased Vascular Response to Norepinephrine in Salt-Sensitive Patients**

Several investigators have observed an exaggerated blood pressure response to circulating pressor hormones, such as norepinephrine or Ang II, in patients with essential hypertension and have postulated that this mechanism may contribute to the maintenance of hypertension. Others, however, have shown no difference in the vascular response to vasoconstrictors between hypertensive and normotensive subjects. The reasons for these discrepancies are not clear, but they may be largely due to a lack of homogeneity of the populations studied in relation to age, race, and dietary NaCl intake. Ziegler et al observed that during stepwise norepinephrine infusion, plasma norepinephrine levels were lower in hypertensive patients than normotensive subjects. When norepinephrine sensitivity was determined using changes in plasma levels rather than rates of infusion, these investigators were able to demonstrate increased sensitivity to norepinephrine in the hypertensive patients.

To test the possibility that an increase in vascular reactivity to pressor hormones might contribute to hypertension in salt-sensitive patients, we studied 11 salt-sensitive and 15 salt-resistant patients with essential hypertension while they were ingesting a diet containing 20 mEq/d Na+ or 200 mEq/d Na+. We studied blood pressure responses to increasing doses of norepinephrine and Ang II at the end of each phase. Salt-sensitive patients exhibited a greater blood pressure response to norepinephrine than salt-resistant patients, irrespective of the dietary NaCl intake and whether we took into account the dose infused or the actual plasma levels of norepinephrine achieved during the infusion (Fig 3). The blood pressure response to Ang II, on the other hand, was greater in salt-sensitive than salt-resistant patients during low but not during high NaCl intake. Because salt-sensitive patients usually display suppressed levels of renin, the greater pressor response to Ang II during a low salt diet could be due to upregulation of Ang II receptors. These studies indicate that increased reactivity to the pressor action of norepinephrine may contribute to the maintenance of hypertension in salt-sensitive patients. The increased reactivity appears to be specific for norepinephrine.

Sharma et al observed a greater pressor response to norepinephrine during high NaCl than low NaCl intake, and the pressor response was greater in salt-sensitive than salt-resistant patients. At variance with our studies, however, these investigators observed an increase in blood pressure response to Ang II during low as well as high NaCl intake. The reason for this discrepancy is unclear.

Skrabal et al observed a greater blood pressure response to norepinephrine in salt-sensitive than salt-resistant subjects independent of dietary NaCl intake. However, these investigators did not correlate postinfusion blood levels of norepinephrine with blood pressure response. In addition, they observed a relation between changes in blood pressure response to a high dietary NaCl intake and changes in the ratio of α1 to β1 receptors in platelets of hypertensive patients, suggesting that the rise in blood pressure in response to a high NaCl intake in predisposed patients may be due to enhanced vasoconstriction caused by an increased ratio of α1 to β1 receptors and enhanced sympathetically mediated renal sodium reabsorption.

In normotensive salt-sensitive subjects, Egan et al observed greater forearm vascular resistance than in salt-resistant subjects during a high NaCl diet. The response of forearm vascular resistance to norepinephrine was not different between the two groups and was not affected by the diet, whereas the response to Ang II decreased during a high NaCl diet in salt-resistant but not salt-sensitive subjects.

**Role of the Renin-Angiotensin-Aldosterone System**

The role of the renin-angiotensin system in salt-sensitive hypertensive patients remains elusive. Most of these patients manifest low PRA during baseline conditions as well as in response to volume depletion.
Recent studies have shown that plasma prorenin is inversely related to salt sensitivity of blood pressure in patients with stage 1 hypertension.97

Using multidimensional response surface modeling, Dustan and Kirk1 found that aldosterone and the sympathetic nervous system but not the renin-angiotensin system featured prominently in blood pressure control in salt-sensitive hypertension in human subjects. However, this does not rule out the possibility that local production of renin within the kidneys might contribute to shifting the relation between pressure and natriuresis in these patients. Low-level infusion of Ang II that does not alter blood pressure levels can cause a shift of the pressure-natriuresis relation to the right.98 The antinatriuretic action of Ang II may be due to stimulation of aldosterone secretion or to a direct action on proximal tubular cells.99 Thus, even low elevations of Ang II levels in relation to sodium intake may alter the pressure-natriuresis relation and result in a sustained elevation of blood pressure.

Insulin and Salt Sensitivity

Recent evidence indicates that several patients with essential hypertension manifest insulin resistance and/or hyperinsulinemia.100,101 Insulin resistance in hypertension involves glucose but not lipid or potassium metabolism and is directly correlated with the severity of hypertension. High sodium-lithium countertransport has been shown in patients with essential hypertension and insulin resistance.102 Some investigators have found reduced insulin resistance and hyperinsulinemia, whereas others have observed enhanced glucose tolerance in SHR.105 Chronic infusion of insulin causes a sustained rise of blood pressure in rats106 but not in dogs.107 Acute and chronic infusion of insulin may cause sodium retention.106-110 Stimulate the sympathtic nervous system,111-115 alter cation transport,116,117 and stimulate hypertrophy of smooth muscle cells in the absence of changes in serum glucose.118

These cellular effects of insulin, if present in smooth muscle cells, could underlie the increase in total body sodium and blood pressure in salt-sensitive hypertensive patients. High NaCl intake reduced insulin sensitivity in young normotensive salt-sensitive subjects with a genetic predisposition to developing hypertension but not in salt-resistant subjects.119 An association between hyperinsulinemia and blood pressure sensitivity to NaCl has been shown in young normotensive and borderline hypertensive blacks by some researchers120 but not by others.121 The blood pressure of obese adolescents is salt sensitive, as shown by a shallower slope of the renal function relation, and this sensitivity may be due to the combined effects of hyperinsulinemia and increased activity of the sympathetic nervous system.122 Loss of body weight in obese subjects was accompanied by a decrease in plasma insulin levels and increase in the slope of the pressure-natriuresis relation. In 10 untreated hypertensive patients, on the other hand, Lind et al123 showed that hyperinsulinemia and decreased sensitivity to insulin were most commonly seen in hypertensive patients with low salt sensitivity.

Chronic hyperinsulinemia in Sprague-Dawley rats produced a shift of the pressure-natriuresis relation, but hypertension in these rats was not salt sensitive and not dependent on sodium retention or increased renin secretion.106

Saad et al124 observed a relation among insulinemia, insulin resistance, and blood pressure in whites but not in blacks with hypertension. Because blacks are more likely to be salt sensitive than whites, this casts some doubt on a possible role of insulin in the genesis of salt sensitivity in hypertension, at least in blacks.

Recently, Julius et al125,126 have proposed that insulin resistance may be a consequence of hemodynamic changes caused by sympathetic hyperactivity.

In conclusion, the role of insulin in salt-sensitive hypertension remains to be established.

The Kallikrein-Kinin System

A reduction in urinary kallikrein excretion has been demonstrated in both clinical and experimental hypertension,127,128 and this reduction correlates with the severity of hypertension.129 In addition, urinary kallikrein excretion is lower in black than white patients with essential hypertension.130,131 Urinary excretion of kallikrein is also reduced in SHR with established hypertension.132-134 This has led to the suggestion that a blunted activity of the vasodilator renal kallikrein-kinin system may be partially responsible for the Na+ retention and may participate in the pathophysiology of hypertension.

Urinary Eicosanoids

Certain prostaglandins have natriuretic properties,135 but their role in the normal regulation of sodium excretion remains undetermined. In rats, excess dietary salt induces the kidney epoxygenase.136 Products of arachidonate metabolism produced by a cytochrome P-450-dependent monooxygenase system are inhibitors of Na⁺,K⁺-ATPase in the thick ascending loop of Henle cells.137 Thus, a deficiency of this substance could contribute to the resetting of the renal function curve and the development of hypertension. Treatment of rats on a high salt diet with clotrimazole, a cytochrome P-450 epoxygenase inhibitor, produces a significant increase in mean arterial pressure. The DR phenotype responds to excess dietary salt with a twofold induction of its renal epoxygenase activity, whereas DS rats demonstrate no significant increases in their renal hypoxygenase activity.138 Long-term induction of renal fatty acid ω-hydroxylase with clofibrate prevents the development of hypertension in DS rats.139

The production of thromboxane B₂ by renal cortical microsomes is increased in SHR, and administration of thromboxane synthetase inhibitors may increase papillary blood flow and retard the development of hypertension.140,141 On the other hand, urinary excretion and papillary tissue content of PGE₂ are reduced in SHR.142 DS rats also manifest lower urinary excretion of PGE₂ compared with DR rats, which may contribute to blunting the pressure-natriuresis relation in these rats.143,144

The role of prostaglandins in salt-sensitive patients with hypertension remains to be established.

Atrial Natriuretic Factor

Atrial natriuretic factor (ANF) has diuretic, natriuretic, vasodilator, sympatholytic, and renin- and aldosterone-suppressing activities.145,146 Thus, ANF is an important regulator of sodium volume status and blood
pressure. This raises the possibility that hypertension, and particularly salt sensitivity, might be a consequence of reduced secretion or action of ANF.

However, the role of ANF in the pathophysiology of hypertension and salt sensitivity has not been well established. Most studies have shown that serum levels of ANF are increased and that high NaCl intake causes a normal or exaggerated rise in plasma ANF in patients with essential hypertension.\textsuperscript{147,149} Increased serum concentrations of ANF were also demonstrated in adult SHR compared with Wistar-Kyoto (WKY) rats\textsuperscript{150} and in DS compared with DR rats.\textsuperscript{151} The increased secretion after salt loading might be due to volume expansion and stimulation of atrial stretch receptors.\textsuperscript{152} Increased concentrations of ANF have been shown by some researchers, particularly in salt-sensitive low-renin essential hypertension, and this may represent an adaptive response to minimize the increase in blood pressure during salt loading.\textsuperscript{153} Some have suggested that ANF may be responsible for the exaggerated natriuretic response to volume expansion in hypertension,\textsuperscript{154} but this notion is not universally accepted.\textsuperscript{155}

Other studies point to the possibility that a defect in ANF secretion might contribute to the development of hypertension. Blockade of endogenous ANF with specific monoclonal antibodies increases the severity of hypertension in stroke-prone SHR and deoxycorticosterone acetate--salt rats.\textsuperscript{155} Salt loading stimulated ANF release into the plasma of WKY rats but not SHR, suggesting that the exacerbation of hypertension seen in NaCl-loaded SHR may be related to impaired ANF release.\textsuperscript{156} Chronic ANF infusion via osmotic mini-pumps prevented the increase in arterial pressure in response to a high NaCl diet in salt-sensitive SHR but had no effect on blood pressure in rats fed a normal salt diet.\textsuperscript{157} Niumura \textsuperscript{158} observed attenuated release of ANF caused by sodium loading in salt-sensitive essential hypertension, and recently, we have observed a paradoxical decrease in the secretion of ANF during 7 days of NaCl loading in salt-sensitive compared with salt-resistant patients with hypertension.\textsuperscript{159}

All these studies suggest that a deficiency in circulating endogenous ANF may play a role in the NaCl-sensitive component of hypertension in SHR and patients with essential hypertension.

Further studies are needed to ascertain the role of ANF in the pathophysiology of salt-sensitive hypertension. The use of inhibitors of ANF, such as the endopeptidase 24.11, may help clarify the pathogenetic role of these peptides in hypertension.

Cellular Transport Characteristics, Intracellular Ions, and Salt Sensitivity

Several abnormalities in cellular transport have been described in patients with essential hypertension. It remains to be determined whether these abnormalities are responsible for the development of hypertension, represent a simple association, or are a consequence of hypertension or one of its pathophysiological mechanisms.

The Na$^+$ Pump

Increased intracellular concentrations of Na$^+$ have been shown in erythrocytes, leukocytes, and lymphocytes of hypertensive patients. The Na$^+$ pump maintains Na$^+$ and K$^+$ gradients across cell membranes by an electrogenic and active transport, and this pump is inhibited by cardiac glycosides, such as ouabain. It has been proposed that in predisposed subjects, high NaCl intake may lead to sodium retention, resulting in increased secretion of a circulating inhibitor of the Na$^+$ pump.\textsuperscript{160-165} This factor, on one hand, would increase natriuresis and reestablish sodium balance; on the other hand, it would cause sodium and calcium accumulation in vascular smooth muscle cells, leading to increased contractility. An increase in [Ca$^{2+}$]$,\textsubscript{i}$ in sympathetic nerve terminals could increase norepinephrine release and blood pressure.\textsuperscript{166-168}

This notion has led many investigators to study the Na$^+$,K$^+$-ATPase activity and Na$^+$ pump density in cells isolated from hypertensive patients. In addition, an exhausting search has been undertaken to detect circulating inhibitors of the Na$^+$ pump, with conflicting results. Several studies have shown that the activity of the Na$^+$ pump (determined by the rate constant of ouabain-sensitive Na$^+$ efflux) is suppressed in patients with hypertension; several others, however, have failed to find any abnormality.\textsuperscript{169} In one large study of 247 subjects, a negative correlation was found between blood pressures and serum concentrations of Na$^+$,K$^+$-ATPase activity and a positive correlation between blood pressure and intracellular Na$^+$. Blacks appear to have lower levels of ouabain-sensitive cation transport in red blood cells than whites, and it is possible that pump suppression may predispose blacks to salt sensitivity and hypertension. The $V_{\text{max}}$ of Na$^+$,K$^+$-ATPase activity was found to be decreased in erythrocyte membranes of Nigerians with newly identified essential hypertension.\textsuperscript{170}

Several investigators\textsuperscript{50,171-174} have described increased serum and urine levels of Na$^+$,K$^+$-ATPase inhibitors in essential hypertension. The plasma from salt-sensitive patients showed significantly higher levels of Na$^+$,K$^+$-ATPase inhibitors and plasma norepinephrine, and these two factors were significantly correlated.\textsuperscript{50} Another study showed a direct correlation between salt-sensitivity index and changes in plasma Na$^+$,K$^+$-ATPase inhibitors and an inverse correlation with fractional excretion of lithium.\textsuperscript{172} Dichtchekenian et al\textsuperscript{173} observed higher serum levels of digoxin-like factor in salt-sensitive than salt-resistant patients with hypertension and a significant correlation of those levels with blood pressure; however, a high NaCl diet failed to increase the serum levels of the digoxin-like factor in both groups of patients. Songu-Mize et al\textsuperscript{174} showed very low binding affinity for ouabain in erythrocytes from black girls with hypertensive parents.

Despite all these studies, however, a cause-effect relation between inhibitors of Na$^+$,K$^+$-ATPase activity and salt sensitivity has not been conclusively established.

Na$^+$-K$^+$-Cl$^-$ Cotransport

This system cotransports Na$^+$ and K$^+$; it is electrically neutral because it also transports Cl$^-$ and is inhibited by furosemide. In several mammalian cells, such as vascular smooth muscle cells and renal tubular epithelial cells, the transport is in an inward direction; erythrocytes, on the other hand, have this transport in an outward direction.

Abnormalities of erythrocyte Na$^+$-K$^+$ cotransport have been described in patients with essential hyperten-
sion as well as in rats with genetic hypertension, but the evidence in the literature is conflicting. Some researchers have shown a decrease and others an increase in the $V_{\text{Na}}$ of the Na-K cotransport system. Some have shown a direct relation between severity of hypertension, decrease in venous compliance, and the $V_{\text{Na}}$ of the Na-K cotransport. The reasons for these conflicting data are not readily apparent. Cusi et al have shown a bimodal distribution of the Na-K cotransport in hypertensive patients, 75% manifesting a distribution similar to that of normotensive subjects and 25% manifesting a distribution into higher levels. Patients with high Na-K cotransport had lower PRA and fractional urinary acid excretion, suggesting an increase in proximal tubular reabsorption; glomerular filtration rate and urinary sodium and potassium excretions were similar to those of normotensive individuals. These patients also had greater blood pressure falls in response to furosemide than normotensive subjects or hypertensive patients with normal Na-K cotransport.

Similarly conflicting are the data on the effect of different dietary NaCl intakes on this transport system. Some researchers have found no significant effects of changing dietary NaCl intake on red blood cell Na-K cotransport. However, Canessa et al observed lower $V_{\text{Na}}$ and $K_m$ values in hypertensive patients on a low compared with a high NaCl diet. The $K_m$ for Na at the inner face was significantly lower in salt-sensitive than salt-resistant black adolescents, suggesting that dysregulation of Na-K cotransport, a system known to mediate sodium transport in vascular smooth muscle cells, may predispose to hypertension during a high NaCl intake. The studies suggest that dysregulation of Na-K cotransport in vascular smooth muscle and endothelial cells may predispose to hypertension in response to a high NaCl intake.

The Na-H Antiport

The Na-H antiport is a ubiquitous cell membrane transport system that promotes an electroneutral 1:1 exchange of intracellular H+ for extracellular Na+ and is activated by an increase in cytosolic proton concentration. This transport system is inhibited by amiloride and its N-substituted analogues. The Na-H exchanger accepts Na as the physiological substrate, but it can also accept Li+ and NH4+. The system is involved in the regulation of intracellular pH, cell volume, stimulus-response coupling, and cell proliferation.

The evidence for a role of the Na-H exchanger in hypertension has been extensively reviewed recently. Several investigators have suggested that enhanced activity of the Na-H exchanger could be responsible for the increase in intracellular Na in vascular smooth muscle cells of hypertensive patients. Canessa et al showed abnormal kinetics of activation of the Na-H exchanger in red blood cells of most hypertensive patients. Increased activity of the Na-H antiport has been shown in cultured fibroblasts from black compared with white normotensive patients. These investigators speculated that an increased Na-H antiport activity in renal tubular cells could provide an explanation for the propensity of black subjects to retain Na and develop hypertension in response to an NaCl load. In eight hypertensive patients, Dudley et al observed that although resting pH in skeletal muscle and unstimulated pH in leukocytes were similar in hypertensive patients and control subjects, Na-H antiport activity during acid loading was increased and acidification in skeletal muscle was decreased in hypertensive patients. Izzard et al. on the other hand, failed to demonstrate an increase in pH in resistance arteries of patients with essential hypertension. Semplicini et al failed to show a significant correlation between the red blood cell Na-H or Li-Na exchangers and proximal tubular Na reabsorption (measured by fractional renal lithium reabsorption) in patients with essential hypertension.

It remains to be established whether the increased activity of the Na-H exchanger is a primary defect or whether it is secondary to alterations of intracellular pH, to vasoconstrictors, or to changes in [Ca2+]. Well-known stimulants of the Na-H exchanger, such as phorbol myristate acetate and ammonium chloride, had no effect or actually decreased [Ca2+] in vascular smooth muscle cells. However, in patients with essential hypertension, the activation of the Na-H antiport could be secondary to an agonist-mediated rise in Ca2+ inside vascular smooth muscle cells and not necessarily a primary defect. Conlin et al have shown that agents such as insulin and norepinephrine, which increase [Ca2+], also activate the Na-H exchanger. This raises the possibility that an increase in norepinephrine or insulin secretion may be responsible for the sodium-dependent rise in [Ca2+], and blood pressure of salt-sensitive patients with hypertension. Moreover, the Na-H antiport activity may not be equally expressed in all cells. If an increase in Na-H antiport activity were to be expressed in renal tubular cells, it could provide an explanation for the propensity of black subjects to retain sodium and develop hypertension in response to an NaCl load. This hypothesis, however, is not supported by recent findings, because all changes in Na-H antiport activity so far reported refer to the isoform NHE-1, which is not involved in epithelial Na transport. Genetic linkage analysis has provided no evidence for NHE-1 to be a candidate gene in hypertension.

The increased activity of the Na-H antiport has been linked to increased cell proliferation. A significant correlation between increased Na-H antiport activity in lymphocytes and left ventricular hypertrophy has been described recently in patients with essential hypertension. Because alterations in the composition of plasma lipids may affect membrane fluidity and the activity of the Na-H antiport, some investigators have speculated that hyperlipidemia may increase Na-H antiport activity in hypertensive patients. A direct correlation has been observed between Na-H antiport activity and serum levels of triglycerides and cholesterol in hypertensive patients. Administration of lovastatin, a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor, decreased Na-H antiport activity in hypertensive patients.

Our current knowledge does not support a role for an abnormality in the Na-H antiport system in the pathogenesis of sodium retention and salt-related hypertension.

Red Blood Cell Na-Li Countertransport

This cell transport system is measured by the exchange rate of external Li for internal Na. It is
believed that this transport system is the same as the Na\(^{+}\)-H\(^{+}\) antiport, even though some investigators believe that the two represent different entities. Both systems mediate an influx of Na\(^{+}\), Li\(^{+}\), and H\(^{+}\), and both systems are inhibited by acidic extracellular pH; however, the Na\(^{+}\)-Li\(^{+}\) countertransport system is not amiloride sensitive. There is a considerable amount of variability in the activity of erythrocyte Na\(^{+}\)-Li\(^{+}\) countertransport in normotensive and hypertensive subjects. However, the weight of evidence indicates increased activity of this transport system in patients with essential hypertension.\(^{68}\) A direct correlation was found between Na\(^{+}\)-Li\(^{+}\) countertransport and body mass index, plasma uric acid, and triglyceride concentrations.\(^{196}\)

Weder et al\(^{199,200}\) showed that patients with the greatest degree of blood pressure elevation in response to a high salt intake manifested a significant rise in the \(V_{\text{max}}\) of Na\(^{+}\)-Li\(^{+}\) countertransport in erythrocytes. In addition, the Na\(^{+}\)-Li\(^{+}\) countertransport activity was correlated positively with peripheral vascular resistance and negatively with renal clearance of lithium, suggesting increased Na\(^{+}\) reabsorption by the proximal renal tubule. These data suggest that an elevated \(V_{\text{max}}\) for red blood cell Na\(^{+}\)-Li\(^{+}\) countertransport could be used as a marker for a hereditary predisposition to salt sensitivity. Redgrave et al\(^{201}\) have described an increased prevalence of high red blood cell Na\(^{+}\)-Li\(^{+}\) countertransport in non-modulator hypertensive patients with a normal or high PRA.

### Abnormalities in Intracellular Calcium

The concentration of [Ca\(^{2+}\)], in platelets of hypertensive patients is greater than in normotensive subjects. In addition, some agonists cause a greater increase in the entry and mobilization of Ca\(^{2+}\) in platelets of hypertensive patients compared with normotensive subjects.

Oshima et al\(^{202}\) have shown that an increase in dietary sodium intake raises intracellular sodium and free cytosolic calcium [Ca\(^{2+}\)], in lymphocytes of salt-sensitive patients with essential hypertension. We have also shown that the rise in blood pressure during a high NaCl diet was associated with increased cytosolic calcium [Ca\(^{2+}\)], in lymphocytes of salt-sensitive patients.\(^{203}\) In salt-resistant patients, on the other hand, there was no change in mean arterial pressure or [Ca\(^{2+}\)] during NaCl loading (Fig 4). In addition, a direct and significant correlation was present between the changes in [Ca\(^{2+}\)] and mean arterial pressure. Administration of nifedipine, a calcium channel blocker, prevented the rise in [Ca\(^{2+}\)], and blood pressure induced by a high NaCl intake. Similar results have been obtained using platelets instead of lymphocytes.\(^{204}\) These studies suggest the existence of a link between dietary NaCl intake, [Ca\(^{2+}\)], and blood pressure in salt-sensitive patients with essential hypertension.

The mechanism or mechanisms whereby a high NaCl intake results in increased [Ca\(^{2+}\)] are unclear. Several investigators have proposed that the Na\(^{+}\)-linked rise in [Ca\(^{2+}\)] may be caused by increased secretion of a circulating inhibitor of the Na\(^{+}\), K\(^{-}\)-ATPase pump. This would increase intracellular sodium and in turn alter the Na\(^{+}\)-Ca\(^{2+}\) exchange system, resulting in increased [Ca\(^{2+}\)] in vascular smooth muscle cells.\(^{59,60}\) Vincenzi et al\(^{206}\) have shown a decreased activity of the calcium pump in red blood cell lysate of hypertensive subjects and have proposed that this might be responsible for the increase in [Ca\(^{2+}\)].

Other studies point to a dialyzable humoral factor in the plasma of hypertensive patients that may elevate [Ca\(^{2+}\)].\(^{197}\) In platelets and neutrophils and sensitize platelets to the calcium-increasing effect of adenosine diphosphate and platelet activating factor.\(^{207-209}\)

We have recently shown that platelet [Ca\(^{2+}\)], in response to arginine vasopressin, thrombin, and an acute saline load was significantly greater in salt-sensitive than salt-resistant patients with hypertension.\(^{210}\)

### Calcium Metabolism and Salt Sensitivity

Evidence has accumulated suggesting a relation between low calcium intake, abnormalities of calcium metabolism, and hypertension in animal models as well as in patients with essential hypertension.\(^{211}\) Salt-sensitive individuals and those with low PRA are more likely to manifest disturbances of calcium metabolism such as low serum ionized calcium and serum magnesium, increased urinary excretion of calcium and magnesium, and elevation of serum parathyroid hormone and vitamin D.\(^{204,212-214}\) They are also more likely to display a reduction in arterial pressure in response to increased dietary calcium intake. In salt-sensitive SHR, high calcium intake prevents the salt-sensitive hypertensive component of genetically mediated hypertension via a sympatholytic mechanism and by increasing the natriuretic and diuretic responses to acute volume loading.\(^{215}\)

High sodium intake causes changes in blood pressure that correlate directly with changes in serum levels of 1,25-dihydroxyvitamin D [1,25(OH)\(_{2}\)D] and inversely with changes in serum levels of ionized calcium and serum phosphate.\(^{216,217}\) In addition, serum levels of a new pressor factor of parathyroid gland origin, the parathyroid hypertensive factor,\(^{218}\) have been shown to be higher in salt-sensitive than salt-resistant patients and in those with low PRA as well as to predict the blood pressure response to NaCl loading.\(^{219}\)

Resnick et al\(^{216}\) have proposed that elevated levels of 1,25(OH)\(_{2}\)D and parathyroid hypertensive factor may stimulate cellular calcium uptake from the extracellular space into smooth muscle cells and be responsible at least in part for salt-sensitive hypertension. Consistent with this hypothesis is the recent demonstration that 1,25(OH)\(_{2}\)D receptors are present in vascular smooth muscle cells\(^{220,221}\) and that 1,25(OH)\(_{2}\)D increases the uptake of calcium in cultured rat aortic myocytes.\(^{222}\) On the other hand, in five patients with essential hyperten-
sion, Kurtz et al.\textsuperscript{233} observed that NaCl loading increased blood pressure without causing any alteration in serum ionized calcium or blood levels of 1,25(OH)\textsubscript{2}D. The relation between dietary calcium, changes in [Ca\textsuperscript{2+}], and hypertension remains elusive.

**Endothelium-Derived Factors and Salt Sensitivity**

Chen and Sanders\textsuperscript{224} have examined the contribution of nitric oxide, the endothelium-derived relaxing factor, to salt sensitivity in young DS and DR rats of the Rapp strain and found that increasing dietary NaCl intake raised nitric oxide activity in DR but not DS rats. In addition, L-arginine and L-citrulline increased nitric oxide production and prevented salt-sensitive hypertension in these rats. In salt-sensitive patients with hypertension, the role of nitric oxide remains to be established.

Because nitric oxide-induced formation of cyclic GMP appears to be a major factor linking changes in renal medullary blood flow with sodium excretion, some researchers have proposed that salt-sensitive essential hypertension could be the result of a deficiency in the production of nitric oxide by endothelial cells.\textsuperscript{225}

**Is Salt Sensitivity Inherited?**

One hypothesis proposed to explain salt sensitivity postulates the existence of an inherited reduction in the ability of the kidneys to excrete a sodium load.\textsuperscript{29,226-228} This hypothesis is supported by crosstransplantation studies\textsuperscript{229-231} showing that transplantation of a kidney from young prehypertensive rats into normotensive rats results in chronic elevation of blood pressure in the latter. In humans, transplantation of a kidney from normotensive donors into patients with severe hypertension and end-stage renal disease (ESRD) due to nephrosclerosis can result in complete normalization of blood pressure.\textsuperscript{232}

Support for the genetic hypothesis comes from animal studies which show that abnormalities in renal sodium excretion and the pressure-natriuresis relation may precede hypertension. The kidneys of 3- to 5-week-old SHR exhibited a blunted pressure-natriuretic response compared with age-matched WKY rats. Similarly, the slope of the pressure-natriuresis relation is altered before the induction of salt hypertension in DS rats.\textsuperscript{233-235} Enhanced reabsorption of water and chloride in the loop of Henle as well as reduced glomerular filtration rate contribute to the resetting of the pressure-natriuresis relations in DS rats.\textsuperscript{236} Support for a genetic transmission of salt sensitivity also derives from the observation that the renin gene cosegregates with blood pressure in Dahl rats.\textsuperscript{237}

Recent evidence indicates that alterations in renal medullary hemodynamics may participate in resetting the pressure-natriuresis relation in very young SHR.\textsuperscript{238-239} On the other hand, the relation between papillary blood flow and renal perfusion pressure appears to be similar in prehypertensive DS and DR rats of the Rapp strain, suggesting that the abnormal pressure-natriuresis relation in this rat strain occurs independently of alterations in renal medullary hemodynamics and probably is due to a primary alteration of renal tubular sodium reabsorption.\textsuperscript{234}

In human subjects, the evidence for a genetic abnormality in the renal ability to excrete an NaCl load as the basis for salt sensitivity is less compelling and primarily based on comparisons of offspring with or without a family history of hypertension. The resetting of kidney function occurs very early or may even precede the development of hypertension, as renal hemodynamic abnormalities can be observed in normotensive offspring of hypertensive patients.\textsuperscript{240,241} Subjects with a positive family history of hypertension exhibit a blunted natriuretic and exaggerated blood pressure response to an acute saline load compared with subjects with a negative family history of hypertension.\textsuperscript{242} To investigate the influence of heredity on blood pressure and the renal excretion of sodium after volume expansion and contraction in humans, Grim et al.\textsuperscript{243} studied 37 pairs of homozygotic and 18 pairs of dizygotic twins under conditions of acute volume expansion or contraction. They observed that urinary sodium excretion, fractional excretion of sodium, and blood pressure response revealed evidence of significant genetic variance. The sympathetic nervous system response to acute volume changes also appeared to be influenced by heritable factors.\textsuperscript{244} In another study, salt-sensitive patients showed a 2.5-fold higher incidence of a positive family history of hypertension than salt-resistant patients.\textsuperscript{21}

Textor and Turner\textsuperscript{245} compared the effect of NaCl loading on the renal hemodynamics of sons of two hypertensive parents with that of sons of two normotensive parents and found greater renal vascular resistance during both a low and high NaCl intake in subjects with a family history of hypertension. In addition, in predisposed patients an acute intravenous saline load caused renal vasoconstriction despite no change in blood pressure or systemic vascular resistance. These studies suggest that alterations of renal hemodynamics may represent an inherited abnormality and be related to the development of hypertension. The inheritance of this trait is supported by the common association of salt sensitivity with the haptoglobin 1-1 phenotype.\textsuperscript{246}

Recent studies in identical twins have shown that salt sensitivity is common in normotensive blacks and that it is under strong genetic control and probably caused by a major gene or at most only a few genes.\textsuperscript{247}

The evidence for inherited transmission of salt sensitivity is largely indirect and does not preclude the possibility that in some patients salt sensitivity may be acquired. Consistent with this possibility is the increasing prevalence of salt-sensitivity in elderly, obese, and diabetic subjects. In addition, secondary causes of hypertension, such as pheochromocytoma or renovascular hypertension, are associated with an intrinsic reduced ability of the kidneys to excrete a sodium load (as expressed by a shift to the right of the pressure-natriuresis or renal function curves), and removal of the primary cause of hypertension completely normalized the renal abnormality in sodium handling.\textsuperscript{248} Thus, one cannot a priori discard the possibility that the abnormality in renal sodium excretion in salt-sensitive hypertensive patients, rather than congenital, might be acquired and secondary to the development of hypertension or to one of its pathogenetic mechanisms.

**Salt Sensitivity and the Risk of Renal Failure**

The incidence of ESRD in patients with essential hypertension is not defined, but earlier data suggested that it is higher in blacks than whites.\textsuperscript{249,251} Recent studies have confirmed these earlier observations and demonstrated that black patients with essential hyper-
tension develop renal insufficiency five to six times more commonly than whites. Rostand et al. have shown that hypertension was the cause of renal failure in 16% of patients with ESRD in a rural county in Alabama. However, the prevalence was 30% in blacks and only 11% in whites. Data from the US Renal Data System show that over the past decade the incidence of ESRD has been steadily increasing, and this increase has been more prominent in blacks. In 1982, 102 new cases per million blacks were reported to develop ESRD from hypertension, compared with less than 20 new cases per million whites. By 1987 the number of blacks with ESRD from hypertension had increased to 143 new cases per million compared with 22 new cases per million whites, giving a black-to-white ratio of 6.6. This ratio was even higher in patients 55 years of age or older. Although these diagnoses were usually based on clinical impressions and were not substantiated by renal biopsies, these data suggest that, despite a better control of hypertension in the US population and a decline in the incidence of strokes and heart disease, the incidence of ESRD due to hypertension appears to be increasing, particularly in the black population. Socioeconomic factors could in part explain this difference. An alternative explanation, however, could be that for any given level of blood pressure elevation, the renal circulation may be subjected to more severe vascular injuries in blacks than whites. This latter possibility is supported by several studies.

Rostand et al. studied the progression of renal disease in 94 patients with well-treated hypertension for a mean follow-up of 58 months. Despite good blood pressure control, a greater number of blacks (23%) than whites (11%) showed a rise in serum creatinine. In a retrospective analysis of the serum creatinine of 10,940 patients who participated in the Hypertension Detection and Follow-up Program, Shulman et al. showed a greater decline in renal function in blacks, men, and those individuals with higher blood pressure values at entry. Finally, Tierney et al. examined the age-related decline in renal function in a large number of blacks and whites and observed that the slope of the decrease in glomerular filtration rate was steeper in blacks than whites. These data are consistent with the notion that hypertension may cause greater renal damage in black than white hypertensive patients.

Like blacks, other groups of salt-sensitive individuals, such as the elderly and those with diabetes mellitus, are more likely to develop renal failure as a consequence of hypertension.

The reasons for the greater susceptibility to injury of the renal circulation in salt-sensitive patients and particularly in blacks remain to be established, but we have proposed that this could be a consequence of abnormalities in the renal hemodynamic adaptation to a high NaCl intake. During a high NaCl diet, salt-resistant hypertensive patients manifested an increase in renal blood flow and decrease in filtration fraction, whereas salt-sensitive hypertensive patients displayed a decrease in renal blood flow and rise in filtration fraction and intraglomerular pressure (Table). These renal hemodynamic abnormalities may provide a mechanistic explanation for the greater propensity of salt-sensitive patients to develop progressive renal failure.

### Renal Hemodynamic Responses to Salt Loading

<table>
<thead>
<tr>
<th>Renal Parameters</th>
<th>Salt-Resistant</th>
<th>Salt-Sensitive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal vascular resistance</td>
<td>−7%</td>
<td>+37%*</td>
</tr>
<tr>
<td>Renal arterial resistance</td>
<td>+5%</td>
<td>+24%*</td>
</tr>
<tr>
<td>Afferent</td>
<td>−21%</td>
<td>+52%</td>
</tr>
<tr>
<td>Efferent</td>
<td>−10%</td>
<td>+21%*</td>
</tr>
</tbody>
</table>

Reproduced from Campese et al. Significantly different from low NaCl diet and from Salt-Resistant. Significantly different from low NaCl diet.

Experimental evidence in rats with spontaneous hypertension supports this notion. Renal function deteriorates faster in salt-sensitive than salt-resistant models of hypertension. SHR and DS rats are two inbred strains genetically predisposed to developing hypertension. Hypertension in SHR develops independently of dietary salt intake, whereas in DS rats hypertension develops only if they are exposed to a high NaCl intake. In younger SHR, the superficial nephrons adapt to the rise in blood pressure, with an increase in renal afferent arteriolar resistance, which protects the kidneys from the adverse effects of arterial hypertension. DS rats, on the other hand, are more susceptible to glomerulosclerosis and proteinuria because they adapt to a rise in blood pressure with a reduction in afferent arteriolar resistance and a rise in glomerular capillary pressure. An impairment of the myogenic responsiveness of the renal afferent arterioles during a high NaCl diet has been confirmed by other researchers in isolated idiopathic kidneys from DS rats. A more accelerated course of renal disease was also observed in other experimental models of salt-sensitive hypertension, such as the deoxycorticosterone acetate–salt hypertensive rat, the uninephrectomized SHR, the Holtzman postsalt model of hypertension, and the Milan strain of SHR.

All these salt-sensitive models of hypertension manifest a decrease in afferent arteriolar resistance and rise in glomerular pressure in response to an increase in blood pressure.

As previously stated, several mechanisms, including increased activity of the sympathetic nervous system, activation of the renin-angiotensin system or insulin, or decreased local production of vasodilator hormones, may underlie the sodium retention and hemodynamic derangements in salt-sensitive patients. One additional possibility could be an abnormal synthesis of renal prostaglandins. Current evidence suggests that prostaglandins contribute to the regulation of renal hemodynamics during activation of the renin-angiotensin system and/or the sympathetic nervous system. Moreover, prostaglandins can modulate the release of renin and norepinephrine.

PGF₂α and PGI₂ antagonize the vasoconstrictor effects of both norepinephrine and Ang II on preglomerular arterioles of rabbit, whereas only PGI₂ and not PGF₂α was effective on the postglomerular arterioles. A rise in [Ca²⁺] stimulates PGF₂α but not PGI₂ release; on the other hand, changes in extracellular calcium ion in vivo may selectively alter renin PGI₂ synthesis. This raises the possibility that a high dietary NaCl intake...
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SALT-SENSITIVITY AND RENAL HEMODYNAMICS

High Dietary Na+ Intake

NE/Dopamine ratio

Salting II

PGH2

PGI2

Renal A II

Hypertension

Intraglomerular Pressure

Glomerular Pressure (Fig 5)

RENAL FAILURE

Fig 5. Flow chart shows possible mechanisms underlying renal hemodynamic derangements in salt-sensitive patients with essential hypertension. NE indicates norepinephrine; 20-HETE, 20-hydroxyeicosatetraenoic acid; PG, prostaglandin; and A II, angiotensin II.

may increase [Ca2+], in renal glomerular arterioles, which in turn may cause a greater increase in PGE2 versus PGH2. This would lead to a relative decrease of preglomerular compared with postglomerular arterial tone and to an increase in filtration fraction and intra-glomerular pressure (Fig 5). This hypothesis, albeit appealing, remains to be tested.

Renal arteries produce 20-hydroxyeicosatetraenoic acid via the cytochrome P-450 pathway, and 20-hydroxyeicosatetraenoic acid is a potent constrictor of canine and rat renal arterioles. It has been suggested that cytochrome P-450 metabolites of arachidonic acid may participate in the myogenic response of renal arteries and the regulation of renal vascular tone. Inhibitors of P-450 attenuate the vasoconstrictor response of the afferent arterioles to elevations in renal perfusion pressure and impair autoregulation of glomerular capillary pressure. Thus, alterations of the P-450 pathway may be responsible for the abnormality in renal hemodynamic adaptation to a high NaCl diet in DS rats.

The role of the P-450 pathway in renal hemodynamic abnormalities in salt-sensitive patients remains to be established.

Microalbuminuria and Proteinuria in Salt-Sensitive Patients

Recent studies have indicated that microalbuminuria is a good predictor of progressive renal disease in patients with diabetic nephropathy. Microalbuminuria in excess of that found in healthy subjects is present in a substantial number of patients with essential hypertension, and a significant correlation between urinary albumin excretion and blood pressure levels has been shown in some studies but not in others. Several epidemiologic studies have also shown that in patients with essential hypertension clinically apparent proteinuria as well as microalbuminuria are independent predictors of cardiovascular morbidity and mortality.

We have recently shown that salt-sensitive patients with essential hypertension manifest a greater amount of urinary albumin excretion than salt-resistant patients. A significant correlation was present between calculated glomerular pressure during high Na+ intake and microalbuminuria and between the changes in glomerular pressure from low to high Na+ intake and microalbuminuria.

These data suggest that microalbuminuria may be a useful predictor of salt sensitivity and renal hemodynamic abnormalities in patients with essential hypertension. It remains to be determined whether microalbuminuria is an expression of or predictor for renal disease in patients with essential hypertension.

Salt Sensitivity as a Cardiovascular Risk Factor?

Schmieder et al observed a positive correlation between NaCl ingestion and left ventricular mass in patients with essential hypertension.

In normotensive and hypertensive rats the myocardial hypertrophy caused by high NaCl intake occurs independently of hemodynamic effects. In both rats and human subjects, dietary NaCl increases left ventricular wall thickness, resembling pressure overload rather than volume overload. Heimann et al showed a higher left ventricular mass in salt-sensitive than salt-resistant hypertensive patients.

The mechanisms for the myocardial actions of NaCl are not clear but may include an increase in the activity of the sympathetic nervous system. A relation between sympathetic hyperactivity, insulin resistance, and coronary risk has been proposed in hypertension. An additional explanation is that salt-sensitive patients may have greater average 24-hour blood pressure levels than salt-resistant subjects. In support of this notion, we have recently shown that salt-sensitive patients with essential hypertension are more likely to manifest a lack of the normal dipping of blood pressure during the night hours. Thus, although the clinic blood pressure was not different, the average nocturnal blood pressure was significantly higher in the salt-sensitive than salt-resistant patients. Salt-sensitive patients also displayed higher serum levels of low-density lipoprotein cholesterol and lipoprotein(a) and lower levels of high-density lipoprotein cholesterol than salt-resistant patients.

An increase in left ventricular mass and hyperlipidemia are now considered major cardiovascular risk factors, suggesting that salt-sensitive patients with essential hypertension may manifest a cluster of hormonal, renal, and metabolic derangements that may potentially lead to renal failure and greater cardiovascular morbidity and mortality.

We have proposed that measurement of urinary albumin excretion may be a useful marker for salt sensitivity as well as a prognostic indicator for renal and cardiovascular complications in patients with essential hypertension.

In conclusion, the mechanisms responsible for hypertension and the adverse renal and cardiovascular risk profile in salt-sensitive patients with essential hypertension remain unclearly defined. Fig 6 presents a hypothesis that interrelates alterations of cellular ion transport with the hemodynamic and hormonal abnormalities observed in salt-sensitive patients. Among the hormonal factors, the sympathetic nervous system may play an important role in the alterations in renal hemodynamics, the insulin resistance, and the NaCl-dependent rise in blood pressure in salt-sensitive patients. All these factors combined may lead to the greater propensity of salt-sensitive patients to develop renal and cardiovascular complications.
with resulting greater-than-normal local production of Ang II. The fact that most of the salt-sensitive patients have low PRA does not rule out the latter possibility. It could also be that high NaCl intake by increasing cytosolic calcium in renal glomerular arterioles may result in stimulation of PGE2 but not PGI2 release. Because PGE2 and PGI2 antagonize the vasoconstrictor effects of norepinephrine and Ang II on glomerular arterioles but only PGI2 appears to be effective on postglomerular arterioles, an imbalance in the production of these two prostaglandins may lead to a relative decrease of preglomerular compared with postglomerular arteriolar tone and result in increased intraglomerular pressure. The issue of bradykinin is problematic and will require further studies with the nonpeptide Ang II receptor antagonists to resolve.

John A. Bartolatus, MD (University of Iowa, Iowa City): Do patients exhibiting a rise in blood pressure with low sodium intake, the counterregulators, also show a paradoxical blood pressure rise after acute diuretic administration?

Dr Campese: I am not aware of any comparison between the effect of a low dietary sodium intake and acute diuretic administration in this regard.

Jorgen S. Peterson, MD, PhD (University of Iowa, Iowa City): You showed that a subgroup of essential hypertensive patients has increased plasma norepinephrine concentration when put on a high sodium diet. What percent of these patients cannot suppress plasma norepinephrine concentration in response to a high sodium diet?

Dr Campese: Most of the published studies, including ours, indicate 30% to 40%. Recall that the concept is to index the plasma norepinephrine concentrations for the urinary sodium excretion, reflecting dietary sodium intake. Thus, an elevated plasma norepinephrine concentration is one that is higher than observed in normotensive subjects at the same level of urinary sodium excretion.

William J. Lawton, MD (University of Iowa, Iowa City): Are patients on chronic digoxin therapy salt sensitive? Do they manifest an increase in cytosolic calcium concentration and blood pressure when placed on a high salt diet?

Dr Campese: I do not think that there is experimental data to answer this question. We know that cardiac glycosides are natriuretic and kaliuretic when infused into anesthetized animals and that the natriuretic response is linearly related to inhibition of Na+,K+-ATPase in the dog. There is no evidence that chronic administration of digoxin increases blood pressure. This, however, does not invalidate the concept, because it may be quite different to have an endogenous release of ouabainlike factors in the presence of other hemodynamic and hormonal changes than to administer those compounds in otherwise normal animals or human subjects. Measurements of plasma concentrations of ouabain in salt-sensitive and salt-resistant patients have not been reported.

Annette Fitz, MD (University of Iowa, Iowa City): Regarding the effect of angiotensin-converting enzyme inhibitors on effenter arteriolar constriction in salt-sensitive patients: Is the effect due to bradykinin or prostaglandins, or do these patients have a more active renin-angiotensin system that fails to suppress after salt loading?

Dr Campese: It could be any of these possibilities. There could be an impaired suppressibility of the renin-angiotensin system in response to an NaCl load,
ing a daily sodium intake of 10 to 20 mmol. Increases in the plasma concentration of counterregulatory hormones, such as norepinephrine, occur with a dietary sodium intake of less than 50 mmol. Because in clinical practice it is difficult to lower daily sodium intake below 50 mmol, I doubt that the increase in blood pressure observed in counterregulators as a result of salt restriction is of great clinical significance. The same is probably true for the observed rise in plasma lipids during dietary salt restriction.

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Salt sensitivity in hypertension. Renal and cardiovascular implications.

V M Campese

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