Corcoran Lecture: The Case For or Against Salt in Hypertension

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Arthur Curtis Corcoran, MD
(1909–1965)

Tribute and Prelude to Corcoran Lecture of 1988

Dr. Corcoran was my mentor during my research fellowship at the Cleveland Clinic Research Division from 1948 to 1951. I owe him much because, in addition to being a good and kind friend, he had deep concern for my development as a clinical investigator. My recent studies, which form part of the accompanying lecture that was given at the 1988 meeting of the Council for High Blood Pressure Research, are an extension of his work and research interests and bear public witness to my gratitude.

Arthur Curtis Corcoran was born in Waterloo, Quebec, in 1909. He attended McGill University from which he received an M.D. degree in 1934. After 2 years of training at the Montreal General Hospital, he went to the Rockefeller Institute where he met Irvine Page. The next year they moved to the Lilly Laboratory for Clinical Research in Indianapolis. There they were joined by Robert Taylor. Thus was formed the famous investigative team of Page, Corcoran, and Taylor that was responsible for many important contributions to the then-new field of hypertension research. In 1944 they established the Research Division of the Cleveland Clinic, which was the first multidisciplinary research team organized to attack a single problem. In 1960, Dr. Corcoran became Director of Medical Education at St. Vincent’s Hospital in Cleveland, later moving to the University of Michigan. He suffered from coronary heart disease, which caused his death in 1965.

Everyone called him “Core.” He was a lovable man with a fine sense of humor and a deep knowledge of language and literature. He collected rare books and the nonmedical writings of physicians. These latter he formed into a book entitled “A Mirror up to Medicine,” published by Lippincott in 1961.

As a scientist he was basically a renal physiologist. It is hard to realize from our 1988 perspective how little was known about the kidney in the 1930s before Homer Smith devised the concept of renal clearance and developed techniques for measuring renal blood flow and glomerular filtration rate. Corc adopted these techniques and most of his major contributions concerned renal hemodynamics in both experimental and clinical conditions.

Corc had a great interest in salt hypertension and also in the adrenal cortex. His interest was natural. Not only was the role of salt in hypertension exciting much work in both experimental and clinical forms of hypertension, but also the possibility of adrenal cortical abnormalities had been suggested. Corc investigated both problems by studying low sodium diet therapy and by developing a method for measuring urinary corticoids, not knowing how many there were and which ones were important. This herculean task came to naught, but that did not diminish his interest in the possibility that the adrenal cortex participates in hypertension. After all, even before aldosterone was discovered, Georges Masson, also of the Cleveland Clinic, showed that the administration of renin to rats caused hypertrophy of the zona glomerulosa of the adrenal cortex. Their many publications that followed that observation reported results of ringing the changes of renin, deoxycorticosterone acetate (DOCA), and salt on experimental vascular disease. Corc participated in these studies and in the subsequent formulation of the concept relating the renal pressor system and adrenal cortical hormones to hypertensive vascular disease.
Salt intake in excess of body needs has long been considered a factor in the genesis and maintenance of human hypertension; the mechanism is salt retention due to faulty renal excretory efficiency. This discussion reviews clinical studies that make a case either for or against the salt hypothesis. Included is a summary of recent experiences with 4 days of salt depletion and 3 days of salt loading in 96 normotensive control subjects and 40 hypertensive patients. These studies were done to test the hypothesis that salt-sensitive blood pressure changes are quantitatively related to sodium balance. However, we found no statistically significant relation between arterial pressure changes and sodium lost during salt depletion or retained during salt loading. The failure of that hypothesis prompted a study of the known factors that control arterial pressure by using multidimensional response surface modeling for changes produced by salt loading. The analysis indicated that in these experiments salt-sensitive blood pressure changes of hypertensive patients were controlled differently than those of normotensive subjects. In the hypertensive group, the changes were highly predictable by combinations of variables, which featured plasma aldosterone, norepinephrine, and epinephrine. In the normotensive group, the changes were less predictable; fewer of the factors were involved, and plasma renin activity was the featured variable. These findings and results of studies done over the past 50 years indicate that salt-dependent hypertension is controlled by many factors and is not a strict correlate of salt intake. (Hypertension 1989;13:696-705)

Investigation into the mechanisms of salt restriction for reducing high blood pressure was a major focus for hypertension research in the 1940s. Another interest was in the adrenal cortex, although ignorance about its hormones and lack of techniques for measurement hampered study.

At that time no one considered that life-long restriction of sodium intake might prevent hypertension. That suggestion came later when epidemiological studies had shown differences in prevalences of hypertension between cultures that came to be ascribed to differences in salt intake, and now several groups have recommended a reduced sodium intake to prevent hypertension.1-3 Imbedded in this recommendation seems to be the conviction that the amount of sodium retained with the usual U.S. salt intake (about 10 g/day) is quantitatively related to arterial pressure.

This discussion will give some of the background for the current focus on the importance of salt in the genesis of hypertension and for the suspected role of the adrenal cortex in that importance. It will describe studies of the effects of manipulating sodium intake in hypertensive patients and normotensive subjects; these studies found no quantitative relation between sodium balance and arterial pressure and, with multidimensional response surface modeling, demonstrated the multifactorial control of salt-sensitive blood pressure changes. To honor Dr. Corcoran, aldosterone as a direct determinant of those changes will be highlighted.

Background
Salt and Hypertension
Salt-sensitive hypertension is a reality, although there is not solid information as to its frequency. Also, we have little evidence that a high salt intake raises the blood pressure of normotensive people, so we cannot say with certainty that the usual salt intake of industrialized societies causes hypertension. However, the importance of habitual salt intake in the genesis of hypertension has been a matter of considerable public health concern over the last 35 years since Dahl and Love4 reported in 1954 that the national prevalence of hypertension was directly related to the average national salt intake. This concern has been expressed through reports from prestigious committees1,2 recommending that Americans reduce dietary salt use to improve blood pressure control of hypertensive individuals and prevent the onset of hypertension in those still normotensive.
More recently, the Intersalt study has suggested that a reduction of salt intake by 100 mM/day would prevent the age-related rise of arterial pressure that so often occurs in industrialized nations.

The conviction that a salt intake above some arbitrary level (e.g., 70 mM/day) is the cause of essential hypertension has a long and interesting history: long, that is, if one takes as evidence the 2,000 BC report of Ch'i Po to the Yellow Emperor that “salt hardens the pulse.” The modern era of this concern could be said to begin in 1904 with the report of Ambard and Beaujard who, working with the famous Widal, found that salt restriction lowered pressure. They concluded that an inability to excrete salt had the potential for causing hypertension. In the 1920s, Frederick Allen used low sodium diets for treating hypertension, but he thought that salt elevated pressure only in people who had renal vascular disease.

In the 1940s Kempner simulated much interest in low sodium diet therapy through use of a rice-fruit diet that not only reduced sodium intake drastically but also protein. Grollman et al then showed that the depressor action was due to salt restriction—not sodium and protein, as Kempner had maintained—by providing a diet low in sodium but of adequate protein intake using the low sodium milk, Lonolac.

For the next 10 years there was intense interest in the mechanisms of low sodium diet therapy. Although these were not defined, the studies did provide information concerning the physiological and biochemical effects of a negative sodium balance. First, it was found that rigid sodium restriction reduced arterial pressure to normal or near normal in about 50% of hypertensive patients. The investigators were, however, unable to distinguish those people who benefit from such treatment without a trial, nor is this possible today. One major accomplishment was the demonstration that such diets decreased plasma volume, extracellular fluid volume, and total exchangeable sodium regardless of the effect on blood pressure. Sodium balance was in some way responsible for the antihypertensive effect because salt replacement in the responders returned pressure to control values. The interest in low sodium diets ended rather abruptly in the 1950s when antihypertensive drugs became available particularly in regard to the pressor effect of salt.

Two situations, one a report and the other a conclusion, are probably responsible for the current interest in the role of salt in the genesis of hypertension. The first was the report by Dahl and Love in 1954 that the prevalence of hypertension of five population groups—Alaskan Eskimos, Marshall Islanders, Americans, Southern Japanese, and Northern Japanese—was positively correlated with average daily sodium intake. The other was the conviction developing in the 1970s that enough is known about causative factors of hypertension to mount programs of prevention, because results of epidemiological studies had strongly suggested a role for dietary salt in pathogenesis.

The development of this conviction is not surprising because those epidemiological studies had shown a clear difference in the prevalence of hypertension and in salt intake of industrialized versus primitive societies, with the latter having little hypertension and a low salt intake as opposed to the former. In spite of the fact that intrapopulation studies had rarely shown a relation between salt intake and blood pressure, the conviction was further strengthened by reports showing rises in pressure when salt was fed to a few diabetic children and one adult and the relief of hypertension in one man when he discontinued using large amounts of sodium bicarbonate to control peptic ulcer symptoms. Largely overlooked were the findings of Kirkendall et al, who had fed 400 mM sodium/day for a month to normotensive adults without a change in pressure, and Luft et al, who had administered up to 87 g salt/day to 16 normotensive subjects and had found only two in whom pressure rose slightly above 140/90 mm Hg (141/94 and 143/92 mm Hg), even though all subjects had markedly positive sodium balance.

Patients at risk of becoming hypertensive may be different than the normotensive subjects studied by Kirkendall and Luft. Mark et al studied salt loading in borderline hypertensive individuals and Falkner et al in normotensive adolescents with hypertensive parents, and both found a slight increase in pressure after a month and 2 weeks, respectively. Also, Weinberger et al in their studies of pressure responses to 1 day of salt loading (2 l physiological saline given intravenously) followed by 1 day of salt depletion (a 10 mM salt intake with 120 mg furosemide) found that black subjects and older people more often had a rise in pressure with salt loading than did white subjects and younger people.

Mineralocorticoids and Hypertension

Probably the interest in adrenal cortical abnormalities began in 1942 with the report of hypertension in patients with Addison’s disease treated with DOCA and salt and the description of experimental DOCA-salt hypertension in rats. Perera was convinced of the importance of adrenal cortical hormones in essential hypertension particularly in regard to the pressor effect of salt. Perera and Blood reported that DOCA injections given to hypertensive and normotensive subjects along with 5–10 g salt/day raised pressure only in the hypertensive group. They also found that 1 day of sodium restriction (11–15 mM) produced less weight loss and smaller urine volume in hypertensive than in normotensive subjects. They concluded “that this difference in response may be referable to primary renal changes or, more likely, to changes in the kidney mediated by the adrenal cortex.” Although Bennett had earlier reported a similar difference between hypertensive and normotensive subjects during short-term sodium restric-
tion, Renwick et al.\(^4\) later found no such difference between the two groups.

These studies of the 1940s were effectively eclipsed by the identification of aldosterone,\(^3\) the first description of primary aldosteronism,\(^4\) the suggestion that a substantial proportion of essential hypertension represents occult hyperaldosteronism,\(^5\) the demonstration that angiotensin II is the primary regulator of aldosterone release (see Reference 36 for review), and the finding that uncomplicated essential hypertension is not associated with elevated plasma aldosterone levels.\(^6\) Such patients, however, do not always have normal aldosterone release responses to certain stimuli because, although they have exaggerated increases with intravenously administered angiotensin II, they have a suppressed response to sodium deprivation, although with sodium loading aldosterone levels are the same in hypertensive as in normotensive subjects.\(^7\)

There is, however, compelling evidence that aldosterone (or some salt-active steroid) features in "low renin" hypertension. Woods et al.\(^8\) found that administration of aminoglutethimide, an inhibitor of steroidogenesis, reduced pressure to normal in such patients, and this finding was later confirmed by Taylor et al.\(^9\) Also, in 1950 Davies and Clark\(^10\) described an "endocrine hypertensive syndrome" in which a low sweat sodium was considered to reflect adrenal cortical overactivity.

**Sodium Retention and Arterial Pressure**

The recommendation that the national salt intake be reduced contains the assumption that if a person cannot excrete sodium normally, hypertension results. Ambard and Beaujard\(^6\) were convinced of this in 1904; Borst and Borst-de-Geus\(^11\) restated this in 1963, and Guyton et al.\(^12\) later proposed that a salt-induced rise in arterial pressure occurred for the purpose of promoting natriuresis and normalizing sodium balance.

The hypothesis that sodium retention is quantitatively related to salt-induced increases in arterial pressure has developed over the past several years. Two reports\(^13,14\) from the Cleveland Clinic showed that hypertensive patients whose pressures were normalized by salt depletion retained more sodium when salt loaded and pressure rose than did patients whose pressures were unaffected, or little affected, by the changes in salt intake. This was confirmed by two reports\(^15,16\) from the National Institutes of Health (NIH) that, in addition, showed the amount of sodium retained during salt loading was positively related to the rise in pressure. However, Campese et al.\(^17\) using the NIH protocol, did not find greater sodium retention during salt loading in salt-sensitive hypertensive in comparison with non-salt-sensitive hypertensive subjects. This suggested an unexpected heterogeneity and raised the possibility that not all patients with salt-sensitive hypertension would respond similarly.

**Current Studies**

At the University of Alabama we have continued the study of the effects of manipulating salt intake in hypertensive and normotensive subjects. That part of the study dealing with the relations between sodium balance and blood pressure changes has been published.\(^18\) A detailed analysis of the rest of the data will be published later. The results presented here are those relevant to the case for or against sodium in hypertension. We used two protocols: one in which salt depletion was the first manipulation followed by salt loading (protocol I), and in the other salt loading was done first followed by salt depletion (protocol II). The second protocol was used to determine if the greater sodium retention found in salt-sensitive hypertensive subjects of the Cleveland Clinic and NIH studies\(^13-16\) only reflected the highly artificial condition in which salt loading followed a period of rigid salt restriction, a situation irrelevant for free-living individuals. The studies were carried out in the General Clinical Research Center of the University of Alabama Hospital. All patients were admitted for a 10-day stay after they had signed an Institutional Review Board–approved consent form. The hypertensive subjects were either untreated or had discontinued their drug therapy for at least 1 month before.

Both protocols had a 3-day control period with 150 mM sodium intake per day. In the first protocol, this was followed by 4 days of salt depletion during which subjects ate a 9 mM sodium diet and took furosemide (1 mg/kg in two divided doses) on the first day. This was followed by 3 days of salt loading during which the low sodium diet was continued and each subject received intravenously a daily salt load of 25 ml/kg isotonic sodium chloride over 4 hours between 1 and 5 PM. This supplied 3.88 mM sodium chloride/kg/day. In the second protocol, the sequence was reversed with salt loading following the control period and salt depletion finishing the study. All other aspects were unchanged.

The following measurements were made: brachial arterial pressure and heart rate, 4 times daily; body weight each morning on a sensitive electronic scale; 24-hour urine collections for sodium, potassium, and creatinine excretions; and at the end of each period (either control or sodium-intake manipulation) plasma renin activity, plasma aldosterone, plasma norepinephrine, and plasma epinephrine. Venous blood for these measurements was obtained after at least a half hour of supine rest in the early morning. Plasma volume was measured and expressed in relation to body surface area, and sodium balance was calculated as the difference between sodium intake and 24-hour urinary sodium excretion and was expressed in millimoles per kilogram. Methods used for these analyses have been previously published.\(^18\)

Ninety subjects, 69 normotensive and 21 hypertensive, participated in the first protocol and 46
TABLE 1. Mean Arterial Pressure Responses to Salt Depletion and Salt Loading

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Number</th>
<th>Control</th>
<th>Salt depletion</th>
<th>Salt loading</th>
<th>Control</th>
<th>Salt depletion</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>69</td>
<td>21</td>
<td>84±8</td>
<td>116±15</td>
<td>81±9</td>
<td>110±14</td>
</tr>
<tr>
<td>II</td>
<td>27</td>
<td>19</td>
<td>83±9</td>
<td>104±17*</td>
<td>87±10*</td>
<td>98±7*</td>
</tr>
</tbody>
</table>

Values given are mean±SD. NBP, normotensive control subjects; HBP, hypertensive patients.

*Significantly different from previous period, p<0.01 to <0.0001.

Subjects, 27 normotensive and 19 hypertensive, in the second (Table 1). In the first protocol, arterial pressure of the control group was remarkably stable with changes in sodium intake, whereas in the hypertensive group it fell with salt restriction and returned toward control values with salt loading. In contrast, in the second protocol some normotensive subjects responded, as did their hypertensive counterparts, with a rise in pressure with salt loading and a fall with subsequent depletion (Table 1). This response apparently reflected two different control populations and not the conditions of the study. Twelve normotensive and 9 hypertensive subjects participated in both protocols. When data from these groups were analyzed separately the results did not suggest that the sequence of salt manipulation was important in the blood pressure responses.

As important as the pressure decreases with salt depletion may be, we will focus on the pressure change with salt loading since this would seem to be more relevant to the public health concern over the advisability of restricting sodium intake. In this regard, the group averages obscure a marked heterogeneity of arterial pressure responses. In the first protocol, most normotensive subjects had an insignificant change in pressure when salt loaded, whereas most hypertensive subjects had a rise (Figure 1). In the second protocol, arterial pressure increases occurred more commonly among the normotensive subjects than in the first protocol (Figure 2). A few normotensive subjects had a striking increase, although not as many hypertensive subjects had a rise in pressure as when salt loading had followed salt depletion.

Now we look at sodium balance (Table 2). When salt depletion followed the control period, hypertensive subjects lost significantly more sodium than did the normotensive subjects, but in the subsequent salt loading period, they did not retain more. In the second protocol, when salt loading was the first manipulation, hypertensive subjects retained less sodium than the control group and did not lose more with salt depletion. In these two protocols, sodium balance during salt loading was as heterogeneous as were arterial pressure responses. In Protocol I, when sodium-retaining mechanisms had been stimulated by depletion, all subjects retained sodium—a few by a very little, however (Figure 3). In Protocol II, some hypertensive subjects even had a negative balance, whereas a few of the normotensive subjects were avid retainers (Figure 4).

To answer the question whether the pressure changes were quantitatively related to sodium balance, we calculated Spearman correlation coefficients.49
This method is preferred to the usual Pearson product moment coefficients because it avoids the assumption of linearity inherent in the Pearson coefficients and favors a more general assumption that the two variables move together but not necessarily in a linear fashion. These Spearman coefficients gave no indication of any statistically significant relation between arterial pressure changes and the amounts of sodium lost during depletion or retained during sodium loading. Thus we were forced to conclude that other factors are responsible for the pressure increases and decreases during manipulations of sodium intake.

**Factors Determining Pressure Responses to Salt Loading**

Many systems control arterial pressure and, although Page’s mosaic is widely accepted for normal pressure, no one has determined which factors are responsible for pressure changes produced by manipulating salt intake. Fujita et al suggested that the pressor effect of salt loading occurred because of a deficient production of prostaglandin E₂. Campese et al found that salt loading in salt-sensitive hypertension tended not to suppress plasma norepinephrine as much as in the non-salt-sensitive type. Fujita et al reported a similar finding in a smaller group of patients. However, some of the salt-sensitive hypertensive subjects studied by Campese had a normal response, so it is difficult to believe that all pressor responses to salt are neurogenic in origin.

As noted above, we measured sodium balance every day and at the end of each period of study.
Protocol II
Sodium Balance with Salt Loading

Table 3. Best Predictive Models for Percentile Mean Arterial Blood Pressure Changes With Salt Loading in Hypertensive and Normotensive Subjects

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Number of variables</th>
<th>R²</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertensive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>8</td>
<td>0.90</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>II</td>
<td>9</td>
<td>0.86</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Normotensive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>3</td>
<td>0.18</td>
<td>0.0128</td>
</tr>
<tr>
<td>II</td>
<td>5</td>
<td>0.68</td>
<td>0.0013</td>
</tr>
</tbody>
</table>

Table 4. Hierarchical Arrangement of Variables Affecting Mean Arterial Pressure With Salt Loading As Determined by Multidimensional Response Surface Modeling

<table>
<thead>
<tr>
<th>Values, changes, and interactions</th>
<th>Frequency of appearance</th>
<th>HBP</th>
<th>NBP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma concentrations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma aldosterone</td>
<td>6</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Plasma norepinephrine</td>
<td>5</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Plasma epinephrine</td>
<td>5</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Plasma renin activity</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Plasma volume</td>
<td>3</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Sodium balance</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

HBP: hypertensive patients; NBP: normotensive control subjects.
uals, 2) aldosterone and the sympathetic nervous system feature prominently in blood pressure control of hypertensive individuals under these conditions, 3) the renin-angiotensin system does not have as direct a role in salt-sensitive hypertension as has been thought, and 4) the magnitude of sodium balance is not a decisive factor. In the past, clinical investigation has focused on single abnormalities as characteristic of hypertension. However, Guyton et al. have long shown the complex interrelations of factors that determine arterial pressure. The data that we present here indicate that we can no longer look for single measurements to give us explanations for such complex conditions as salt-sensitive hypertension.

Aldosterone As Determinant of Salt-Sensitive Hypertension

Because this is the Corcoran lecture and because of Dr. Corcoran’s interest in mineralocorticoids, it seems appropriate for this discussion to focus on the mechanism whereby aldosterone plays its role. There is a large body of compelling evidence for a direct role for aldosterone in salt-sensitive hypertension that has come from the laboratory investigations of Friedman and colleagues and of Jones. These effects have been shown for both in vitro and in vivo situations so they cannot be dismissed. Our results with multidimensional response surface modeling that show the importance of aldosterone in control of salt-sensitive blood pressure changes as well as the laboratory investigations of Friedman and Jones provide an explanation for the depressor effects of aminoglutethimide reported by Woods et al. and Taylor et al.

The cumulative results of the studies relating adrenal cortical abnormalities to hypertension are but another step in defining the role of the adrenal cortex, and they provide support for Dr. Corcoran’s intuition of the importance of that role. In the 1951 report of low sodium diet therapy, after noting a lack of quantitative relation between sodium balance and arterial pressure changes, he commented: “Many facts point to a change in the function of the adrenal cortex or to a change in the response of vascular end organs to the effect of its hormones as the primary determinant of sodium responsiveness.”

Then, why are some patients sensitive to the effects of aldosterone and others are not? It seems likely that this is related to differences in membrane structure, probably genetically determined but possibly because of differences in other mechanisms that regulate arterial pressure.

The Case For or Against Sodium

Salt-sensitive hypertension is real even though we do not know its prevalence. The suggestion that reducing sodium intake by 100 mM/day would abolish the age-related rise in arterial pressure is attractive, but the question is whether there is actually enough evidence to support that recommendation. Further, it implies that all rises in pressure with age are salt dependent. Considering the multifactorial control of arterial pressure, that implication is difficult to accept. In fact, there is so much heterogeneity of arterial pressure responses to any stimulus (e.g., manipulating sodium intake) that it is difficult to accept that a considerable reduction in salt intake would eliminate all increases in arterial pressure as people age.

There are many unanswered questions: 1) Does salt feeding raise blood pressure of normotensive individuals? All we have is the experience with a few diabetic children and a few adults. The longest study of Kirkendall was a month in duration and no effect was demonstrated. 2) Does a high salt intake raise pressure of hypertensive individuals? We know that it does when pressure has been reduced with rigid salt restriction, but we do not know whether that is the universal response when salt is added to that already being consumed. The experience of Mark et al. with borderline hypertensive subjects and that of Falkner et al. with children of hypertensive parents suggests that it does, but there is actually very little other information available. 3) Is there a difference in sodium sensitivity? Given the demonstrated heterogeneity of arterial pressure responses to manipulating salt intake, this seems the likely case. The early studies added a usual salt intake to a restricted regimen and noted a rise in pressure. This is a far cry from a stepwise reduction that would probably show that some salt-sensitive hypertensive individuals have reduced pressure with a slight reduction, whereas in others marked restriction is necessary for a depressor effect. 4) Is a 100 mM/day reduction in sodium intake a reasonable goal for free-living people? In a study in England, Sanchez-Castillo et al. found that 83% of salt intake came from processed foods. If that is the case in all industrialized nations, a 100 mM/day reduction may not be an achievable goal. 5) If subsequent studies of low sodium diet therapy confirm that there is no quantitative relation between sodium retention with salt loading and blood pressure change, is there reason to recommend salt restriction for everyone? It would seem better to define those people whose genetic backgrounds have conferred a sodium sensitivity, because for these people some degree of salt restriction is a valid health measure.

These questions indicate that much more information is necessary to provide a logical base for public health recommendations concerning dietary sodium intake.

References

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**KEY WORDS** • salt sensitivity • aldosterone • blood pressure • multidimensional response surface modeling

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