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HARVEY C. GONICK

VOLUME 14

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Preface

How can anyone state categorically that a thought he once had is no longer valid? An idea can be *refuted,* yes, but not *retracted.* . . . In a society run by terror, no statements whatsoever can be taken seriously. They are all forced and it is the duty of every honest man to ignore them.

Milan Kundera, *The Unbearable Lightness of Being*

Arguably, the most dramatic and salutary event to have occurred in the latter half of this century is the cessation of the Cold War restriction on open exchanges of ideas. With the long overdue advent of "glasnost," introduced so recently by Soviet President Gorbachev, we can expect to see an increasing number of important contributions from our Eastern European colleagues in the scientific literature and at international forums. As the editor of this series, I look forward in future issues to including authors whose ideas have not heretofore been disseminated in the West.

At this time, however, I should like to call the reader's attention to some highlights of Volume 14. We are privileged to present a review of the role of erythropoietin in the pathophysiology and treatment of the anemia of chronic renal failure by Drs. Joseph Eschbach and John Adamson, pioneers in this field. In another minireview, Drs. Nancy Curry and Leonie Gordon update selected topics in uroradiology. Nephrologists will find the comparison of the allergic and nephrotoxic potentials of high-osmolality and low-osmolality contrast media of particular interest. Other new contributors to *Current Nephrology* are Dr. Stanley Jordan and his colleagues, who have authored the chapter on the glomerular diseases. Their introductory sections on cell-mediated immunity in glomerulonephritis and cytokines as mediators of glomerular inflammation provide a sturdy skeleton upon which to base our understanding of the immune glomerulonephritides. In the transplant

arena, detailed discussions of the clinical applications of both OKT3 and the exciting new immunosuppressant agent, FK 506, may be found in both the transplantation chapter and the chapter on drugs and the kidney. The latter chapter also introduces us to a new class of pharmaceutical agents, the potassium channel openers, which have potential therapeutic implications for hypertension and diseases associated with vascular contraction.

As always, I wish you pleasant reading.

Harvey C. Gonick, M.D.

Contents

CHAPTER 1

Hypertension

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In this chapter we review recent progress in both the oldest and the newest ways of treating hypertension. For many years dietary sodium restriction was the only nonsurgical method for controlling the ravages of severe hypertension, but when the first effective pharmacologic agents were introduced in the 1950s, and diuretics soon after, sodium restriction became less popular. More recently, the trend to treat people with milder forms of hypertension has revived interest in nonpharma-

cologic modalities of treatment, including sodium restriction. Hypertension is probably a heterogeneous process, and the concept of salt sensitivity has proved to be a useful example of this.

We will also review the evidence that potassium supplementation may not only lower blood pressure, but also have an independent protective effect against stroke.

A third dietary intervention of potential interest is calcium supplementation. The links between sodium and calcium metabolism are increasingly being recognized, although the role of calcium in the hypertensive process is less well understood. Calcium supplementation may lower blood pressure in some individuals.

Sodium balance is under control of the renin-angiotensin-aldosterone system, and in the past few years there has been a significant advance in our understanding of the effects of angiotensin on the kidney, such as the enhancement of proximal tubular sodium reabsorption. This subject is also relevant to the mechanism of action of the angiotensin converting enzyme (ACE) inhibitors.

Finally, we will discuss some of the latest advances in the pharmacologic treatment of hypertension, which include ACE inhibitors, β blockers, and calcium antagonists.

SALT (SODIUM CHLORIDE) AND HYPERTENSION

Dietary Salt and the Blood Pressures of Populations

Over 15 years ago, Dahl proposed that both the incidence of hypertension and the elevation of blood pressure with age in a population were related to the prevailing level of salt intake,[1] and at least since that time, this hypothesis has been the focus of an ongoing controversy. Ideally, the issue should be addressed by long-term interventional studies of salt restriction in normotensive and hypertensive subjects, but studies that have been done have been too short to address issues of prevention. The vast majority of the data addressing the issue is derived from cross-sectional, observational studies within and between populations.

The completion of Intersalt, a study of the relationships of blood pressure and electrolyte excretion in human subjects from 52 centers in 32 countries around the world, has provided the most comprehensive cross-cultural data currently available.[2, 3] Unfortunately, as noted in the editorial accompanying publication of the results, a study can be "definitive without being conclusive."[4] All 10,079 subjects (men and women aged 20 to 59 years) included in the analysis collected 24-hour urine samples which were judged complete. Of the 52 centers, four were located in isolated, "unacculturated" areas and had median urine sodium excretion ranging from 0.2 to 51 mmol/day, while in the remaining 48 centers, median urine sodium excretion ranged from 96 to 242 mmol/day, with only one center having excretion

rates substantially above 200 mmol/day. Thus, the range of sodium excretion among the different centers was relatively narrow, with four extremes at the low end and one extreme at the high end. Earlier findings were confirmed: in the four low-salt centers, blood pressure did not rise with age, and the prevalence of hypertension was less than 5%, while in the other centers the opposite prevailed. When adjustments were made for body mass index, alcohol intake, age, race, and sex, significant relationships between sodium intake and systolic pressure were found in only ten centers, with eight showing positive correlations and two showing negative correlations.

Correlations between diastolic pressure and sodium excretion were significant in six centers: three with positive correlations and three with negative correlations. Overall, the relationship between sodium intake and systolic pressure was statistically significant, although of dubious physiologic significance (a 2.2 mm Hg increase of pressure per 100 mmol sodium/day), while with diastolic pressure it was not. An important finding was that controlling for confounding factors such as potassium intake, body mass index, or alcohol intake weakened the relationships between sodium excretion and blood pressure, suggesting that some of the apparent effect of sodium intake on blood pressure may derive from its role as a proxy variable for other conditions affecting blood pressure. The narrow range of mean sodium intake among the centers may have limited the ability of the researchers to detect an effect of sodium, but it is of interest that societies with uniformly very high salt intakes appear to be rather unusual.

Additional studies have appeared recently from Scotland,[5] Belgium,[6] and China,[7, 8] that show at most small relationships between sodium intake and blood pressure within populations, which weaken even further after accounting for covariates such as potassium or weight.

The Intersalt study found that blood pressure increased with age as a function, albeit weak, of urinary sodium. On the assumption that this association was causal, linear regression modelling utilizing data from all 52 centers suggested that for every 100 mmol sodium ingested per day, diastolic blood pressure would increase by 6 mm Hg and systolic blood pressure by 10 mm Hg over a 30-year period. That this relationship is a good deal more complex than linear modelling can account for is suggested by the fact that a relationship between increasing blood pressure with age and sodium excretion was only seen in subjects over 40 years old.

The limits of what can be learned from cross-sectional surveys seem to have been reached, although no consensus exists regarding their implications for public health policy. A critical issue in the interpretation of these studies is whether the effect of salt restriction is uniform in a population or whether the rather small aggregate effects are the result of large effects of salt in some people and the absence of any effect in others. If the effect is diffuse, even the small changes in blood pressure produced by salt restriction might have important public health consequences,[9] although issues of safety and cost would still have to be addressed.

Salt Sensitivity of Blood Pressure: Intervention Trials

During the past several years, studies have appeared addressing three key issues regarding salt and blood pressure. First is the effect of moderate-to-severe salt restriction in large groups of patients studied over relatively long periods of time. Second, information is beginning to accumulate regarding the dose-response of blood pressure to different levels of salt intake. Third, studies have addressed the feasibility and effectiveness of community-wide interventions which lower salt intake.

The Australian trial of mild sodium restriction (less than 80 mmol/day) was a randomized, placebo-controlled study conducted on 108 subjects who followed low sodium diets for 8 weeks,[10] confirming a previous, smaller, and shorter trial of mild sodium restriction.[11] In these mildly hypertensive subjects (average diastolic pressure, 95 mm Hg), the placebo group had an average urinary sodium excretion rate of 90 mmol/day, while a second group, ingesting 80 mmol slow-release sodium daily, had an average urinary sodium excretion rate of 152 mmol/day during the active phase of the study. The low sodium group had a fall in blood pressure of 6.1/3.7 mm Hg ($P < .005$), while the normal sodium group had an insignificant fall of 0.6/0.9 during the final 4 weeks of the study. As has been found previously, there was great heterogeneity of blood pressure responses in both groups. Multivariate analysis revealed that greater falls in both systolic and diastolic blood pressure in the low sodium group were associated with older age and higher pretreatment systolic blood pressures. The fall in systolic pressure was also associated with decreases in weight during the study. The relationship to pretreatment systolic blood pressure, while not always found, has been suggested by previous analyses.[12]

MacGregor and colleagues have replicated these findings utilizing similar methods of placebo control in a cross-over study of 20 patients.[13] They also found that the hypotensive effect of low salt intake (50 mmol/day) was sustained over 1 year, which are the longest follow-up data available. This study also provided information on the response to three different levels of sodium intake, each maintained for 4 weeks. Stepwise increases of sodium intake, which increased the sodium excretion rate from 49 to 108 mmol/day and then to 190 mmol/day, produced corresponding increases in blood pressure (147/91, 155/95, and 163/100 mm Hg, respectively, on each of the three intakes). Thus there was no threshold level of sodium intake for salt sensitivity of blood pressure, contrary to previous hypotheses.[14] Others have also noted the absence of such a threshold in salt-sensitive subjects.[15] These results suggest that reduction of salt intake as far as is practical, and not merely to very low or even moderate levels, is useful in susceptible individuals.

A recent study has examined the relationship of obesity-related hypertension to salt sensitivity.[16] In this trial, 60 obese and 18 non-obese adolescents were evaluated for salt sensitivity of blood pressure by comparing parameters after 2 weeks