Age as a Function in the Development of Sodium-Related Hypertension

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The populations of the developed nations of the world exhibit an increase in blood pressure with age, while in primitive societies blood pressure remains relatively constant throughout adult life. Hypertension may be a complex of diseases all having the same clinical manifestations but not being caused necessarily by the same factors. A possible common denominator in the development of any chronic elevation of blood pressure is the need for the kidney to increase urine volume to promote sodium excretion and, thereby, prevent a chronically expanded extracellular fluid (ECF). Hypertension may be viewed as a maladaptation of the body in its attempt to maintain homeostasis of the ECF. Man evolved under conditions of relative scarcity of salt and even now can maintain normal body function with an intake of less than 2 g/day.

The high risk person appears to have a hereditary predisposition to a rise in blood pressure in the presence of a high sodium (NaCl) intake. Actually, the degree of rise in blood pressure may be an interaction between the amount of genetic predisposition and the level of sodium and its relation to potassium intake. Recent work in two Massachusetts communities supports this interpretation and suggests that differences in blood pressure distribution may increase with age between a higher and lower sodium community.

Hypertension as a Problem

Hypertension is the most common of the chronic diseases in the United States, afflicting some 24 million people (*1*). Cassell (*2*) has commented that "Despite spectacular advances in elucidating the pathophysiological mechanisms that control blood pressure levels and concomitant improvements in treatment as well as voluminous and enthusiastic research, we are still powerless to prevent the rise in blood pressure that is so characteristic a feature of aging in developed society." Although there is a wide variance in the proportion of the population which is hypertensive in the various nations of the world, it is a major problem in all the developed nations.

High blood pressure may be asymptomatic itself, but ultimately it leads to increased risk of stroke, heart disease, or kidney failure. For about 10% of the cases of elevated blood pressure, specific causes are found, while for the other 90% no clinical basis can be determined (*3*). This latter type with unknown cause is termed essential hypertension.

One need not have blood pressure (BP) at a

hypertensive level to be at a higher risk of dying. Actuarial data from life insurance companies clearly demonstrate that the risk of dying prematurely from cardiovascular complications is markedly increased, even for persons with only slight elevations of BP (*4*). The risk increases sharply at each level of BP throughout the range, with no cut-off point or threshold for increased risk. Therefore, every person should strive to maintain as low a BP as possible.

Blood Pressure Rises With Age

In the developed nations of the world, BP increases with age on a cross-sectional population basis. The frequency distribution for both systolic and diastolic BP tends to shift upward with age in both men and women and spread out, but offers no evidence of segregation into two populations, normotensive and hypertensive (*5*). Consequently, BP may be considered a continuous unimodal biologic distribution with skewing to the right.

The recent National Health Survey provides information about the relationship of BP to age for U.S. white males and females 7-74 years of age. As

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noted in Figure 1, both systolic and diastolic BP for both males and females are generally higher at each succeeding decade. The average rise is 7 mm Hg per decade for systolic BP and 5 mm Hg per decade for diastolic. Black males and females show the same BP levels until adulthood; thereafter they follow the same amount of rise with age but at a higher level than whites. Other developed nations show similar rises in BP with age in their populations, but at higher or lower base levels than the U.S.

It is a striking fact that hypertension is not found in unacculturated societies, nor does BP rise with age as occurs in all "civilized" populations (6–14). Primitive societies do not exhibit a rise in BP with age until they are acculturated and adopt the life style of the developed nations. Many studies (10, 12, 15–17) have been carried out comparing BP of primitive tribes and their more acculturated neighbors. Prior's data (16) comparing Polynesian males in tribes with outside cultural contact against tribes remote from developed areas illustrate the typical finding. Figure 2 indicates that the males from remote tribes show little change in BP with age, while the males in the tribes with cultural contact demonstrate a clear rise of BP with age as well as a higher beginning base level.

Similary Page (17), in a study of six Solomon Island Societies, found BP to be rising with age in females of the three more acculturated populations, but not in the three less acculturated. Weight decreased with age in all of the societies. BP trends were correlated best with sodium intake, with the highest BP levels being found in that acculturated group with the highest sodium intake. Thus, it appears that low BP populations do not possess an

FIGURE 2. Mean blood pressures of similar people living under different degrees of cultural contact: (———) contact; (--) remote. Adapted from Prior et al. (16) with permission.

inherent genetic protection from rising BP, thereby implicating environmental factors as a possible explanation.

Cassell (18) recently reviewed studies comparing natives in their original homeland with their peers who migrated to other areas. He concluded that there were genetic differences in susceptibility to environmental factors. The latter environmental factors being caloric intake, level of physical activity with associated body build, and salt intake. Psychosocial factors, including social stress, were also possibly implicated.

Looking at studies of BP within the U.S., four Chicago cross-sectional studies (19) indicated that the variables most strongly and consistently independently associated with level of systolic and diastolic BP other than age were relative weight, resting heart rate, and plasma glucose 1 hr after oral load. However, the best correlates of current BP are not necessarily the same ones associated with future rise in BP.

Studies indicate that, among hypertensives, an upward trend in BP is present in childhood (20, 21), and children of hypertensive parents have a higher BP and a stronger upward trend than the children of normotensive parents (20). These trends appear to be detectable as early as two years of age (20).

Two longitudinal studies (19) in Chicago as well as several others by Harlan (22) Miall (23), and Paffenburger (24) indicate that current relative level
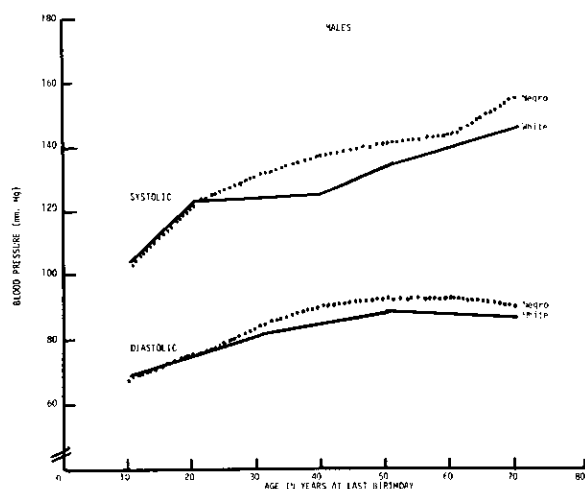
FIGURE 1. Mean systolic and diastolic blood pressure of white and Negro males 7-74 years, by age: United States, 1971-1974. Source: National Health Survey (1).
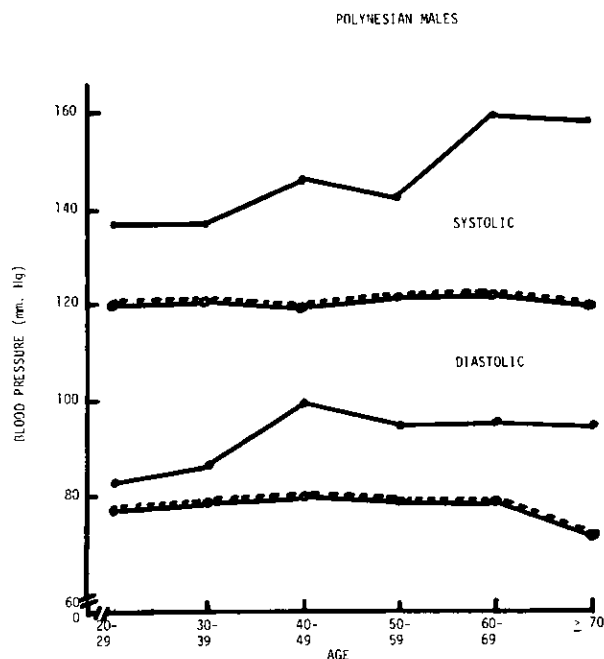
of BP is the best predictor of future BP since an individual tends to maintain his/her relative position on the BP curve over time. Weight gain during early adulthood appears to be another important, although less powerful, predictor (22, 24). High BP seems to result from a complex interplay of factors, not all of which carry equal weight. The evidence taken together indicates that the factors with the strongest association with BP are heredity, age, race, obesity, and sodium ingestion. The remainder of this paper will address heredity briefly, then assess the role of sodium in relation to hypertension, including some relevant studies recently conducted with secondary students in two Massachusetts communities.

Heredity

Animal studies (25-27) demonstrate that heredity plays an important role in susceptibility to salt-induced hypertension. Dahl (26), in selective breeding experiments, isolated sodium-sensitive and sodium-resistant rat strains that do or do not develop hypertension in response to ingestion of similar amounts of salt (NaCl). Neither sodium-sensitive nor sodium-resistant rats were found to develop hypertension if salt intake was kept to a minimum. When genetically unrelated rats were used in sodium loading experiments, the incidence and severity of hypertension was found to vary directly with the salt (NaCl) concentration of the diet (28).

Familial aggregation of BP at all levels of pressure in human studies has been documented in both adults and children (29). Among first degree relatives the correlation coefficients are on the order of 0.16 to 0.29. Among children and their siblings the correlations reach 0.32 to 0.34 and for adult sibs about 0.30. However, families share their environment as well as their genes, such that the demonstration of familial correlations does not necessarily require the operation of genetic influence.

Additional studies have compared adopted children, natural children, and the shared parents in the same families (20, 30). The correlation of the natural children's BP with the natural parents' was 0.34 while the relationship between the BP of adopted children and their adoptive parents in the same families was only 0.03. Perhaps even more important evidence derives from twin studies. Feinlieb (31) found a correlation coefficient r of 0.55 between blood pressures of monozygous twins but only an r of 0.25 between dizygous twins. There is then a general consensus that a genetic factor is important in determining susceptibility to hypertension (32), although the exact mode of inheritance has not been

clearly established. Most studies favor the interpretation that a polygenic, rather than single gene, mode of inheritance best explains the existing data on familial occurrence of hypertension (32, 33). However, it should be noted that even in monozygous twins heredity alone could account for a maximum of 30% of the variation in BP, while among other siblings only about 10% of the variability is accounted for. This evidence suggests environmental factors as being important above and beyond any hereditary component.

Sodium Intake

The part played by salt in hypertension was suspected earlier than 2300 years B.C. by a Chinese physician, the Yellow Emperor, who noted that indulgence in salty foods hardened the pulse and that this predisposed toward apoplexy with aphasia (34). Some 4000 more years passed before Ambard and Beaujard (35) in 1904 reported on the importance of chlorite retention in hypertension. Weinsier (36) drawing on the work of Dahl (28) and Isaacson (37), illustrated the association between salt intake and prevalence of hypertension in today's world (Fig. 3).

Higher intake of salted foods among these groups correlated with higher prevalence rates of hypertension in what could be interpreted as a dose response relationship. On an aggregate level, for every 6 g increase in average daily sodium intake, there appears to be a 10% increase in the prevalence of hypertension. However, the association between sodium dietary intake and blood pressure does not hold up within populations.

This lack of significant correlation in intrapopulation studies has been interpreted as evidence
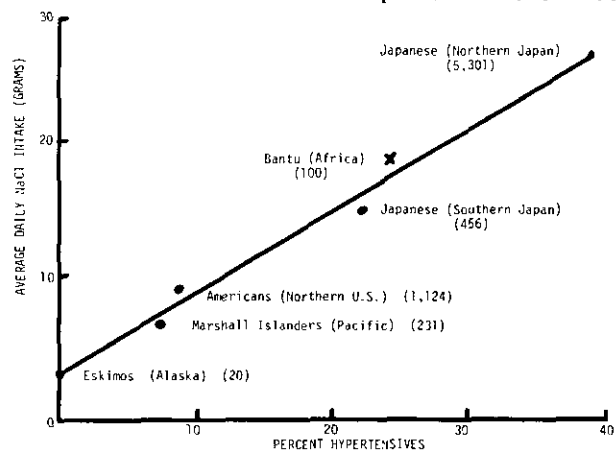

FIGURE 3. Comparison of the prevalence of hypertension among various populations according to their average salt (NaCl) intact. Source: from Weinsier (36), based upon work by Dahl et al. (28) and Isaacson et al. (37).

against an important etiologic role for sodium in human hypertension. This lack of correlation, however, can be equally well explained by the presence of widely variable genetic susceptibility to the effects of sodium on blood pressure plus a high average sodium intake in the population in question. Under these circumstances, variation in blood pressure may be related more to the genetic factor than the sodium intake.

For generations, many hearty people such as the Eskimos, certain Chinese, American Indians, and African tribes customarily used no exogenous salt in their diet (38). Despite diverse environmental conditions, they subsisted on sodium chloride intakes averaging only 1–2 g/day, which was more than sufficient for their metabolic needs, including growth. This amount is readily available in salt unsupplemented diets. Recent estimates of mean daily intake of salt by adult Americans is on the order of 5–15 g/day (39).

There is considerable evidence suggesting that excess ingestion of salt is involved in the genesis of primarily hypertension. In man the evidence is indirect (36, 40–48), but in the laboratory animal the evidence is direct and unequivocal (25–27, 49–61). The extensive research with rat, chicken, rabbit, dog, and monkey models may be summarized as follows: (1) the greater the ingestion of salt, the more severe the hypertension; (2) the younger the animal at the time it is fed a high salt diet, the more sensitive it is to developing rapid hypertension; (3) even a brief exposure (2–6 weeks) to a high salt intake early in life may influence the later development of permanently elevated BP; (4) genetic factors influence the individual's response to salt (NaCl) intake.

Although there is not a general consensus as to the exact mechanism by which excess sodium ion induces hypertension in laboratory animals, considerable evidence has accumulated in the last few years indicating that it involves the regulatory mechanism governing the renal excretion of sodium. Dahl and his co-workers (62) have demonstrated that transplantation of kidneys between sodium-resistant and sodium-sensitive rats results in a BP decrease in that rat receiving the sodium resistant kidney.

Physiological Basis for Salt as a Factor in the Rise of Blood Pressure with Age

Salt ingested in the diet is distributed predominantly to the extracellular space. The concentration of sodium in the extra cellular fluid (ECF) is maintained within narrow limits through regulation of the

excretion of water by the kidney, under the influence of endocrine, cardiovascular, and autonomic regulatory mechanisms. The pathogenesis of hypertension is hypothesized by Freis (39) to operate as follows. Homeostasis of the ECF is maintained by a balance between salt and water intake and urinary output. The urinary output depends in part on the level of arterial blood pressure, this relationship differing from individual to individual depending on the intrinsic capacity of the kidney to handle salt and water loads. Therefore in essential hypertension there may be an inherited defect in the handling of sodium such that the kidney requires a higher than normal perfusion pressure to maintain ECF homeostasis in the presence of a high sodium intake. Evidence also indicates that frequently repeated elevations of BP will eventually lead to structural changes in the resistance vessels so that the wall is thickened and the lumen is correspondingly narrowed (63). BP then cycles upward in a vicious circle. Such a process could well be further amplified in the presence of an expanded ECF.

The renin-angiotensin-aldosterone (RAA) system has been much investigated in its relation to hypertension (64–68). Although it is clear that defects in the production of any of these elements can affect the ability of the body to adjust the resistance of the circulatory system and/or blood volume, the RAA system is thought to be capable only of short-term adjustments to maintain homeostasis of these systems and any continued elevation of sodium eventually overwhelms the RAA system. Experiments with animal models (69) and with inhibitors of the RAA system have indicated that with depletion of the sodium ion, BP becomes dependent on the RAA system. However, with sodium loading, the RAA system is depressed and the BP becomes dependent on the sodium ion. Therefore, in the presence of excess sodium intake, BP must gradually rise to promote increased urine volume and sodium excretion to prevent a chronically expanded ECF. The level of BP required to produce the necessary diuresis depends upon the ability of a particular kidney to excrete an excess of sodium which varies from individual to individual and which probably diminishes with age. BP gradually rises with age as a compensatory reaction for maintaining homeostasis of the ECF.

Hypertension then may be viewed as a maladaptation of the body in its attempt to maintain homeostasis of the ECF. Man evolved under conditions of relative scarcity of salt and even now can maintain normal body functions easily with an intake of as little as 1 g salt/day. The current high sodium intake of modern society essentially overloads man's adaptive capacity. In a population with varying de-

grees of susceptibility, genetically determined, the higher the sodium intake of the population, the larger the proportion whose adaptive capacity is ultimately stressed.

Sodium/Potassium Ratio

Potassium chloride intake appears to offset the hypertension effect of a large salt intake. Dahl, in his experiments with rats (70), discovered that maintaining a constant sodium intake while increasing the levels of potassium intake reduced BP; that the dietary Na/K ratio affects the severity of hypertension; and that sodium exerts a stronger influence than that of potassium.

In human populations, the Na/K ratio in urine is higher in individuals from the upper end of the BP distribution. Langford (71) found that both the blood pressure and the Na/K ratio were higher for black than white girls.

The average American diet, high in fats, meats, and dairy products, and well salted, has a high Na/K ratio of approximately 1.5/1 and ranging up to 6/1. Kempner's rice-fruit diet has a Na/K ratio of 1/20 (30). Man has demonstrated adaptation to the low-sodium, high-potassium intake, whereas healthful adaptation to the high-sodium, low-potassium, Western-type diet remains to be seen.

The remainder of the paper will briefly review the work currently being conducted at the University of Massachusetts, Amherst, on sodium in the public water supply and its possible relationship to BP and changes in blood pressure.

Methods

The strategy was to compare BP of high school tenth graders in two geographically contiguous communities (Table 1) which were markedly similar with regard to factors related to BP: size, income, education, ethnicity, and recent rate of growth. However, the two communities had sodium levels in the public drinking water of 8 mg/l. and 108 mg/l., respectively. These differences in sodium levels had

Table 1. Socioeconomic comparisons of the high- and low-sodium communities.[a]

Characteristics	High-sodium community	Low-sodium community
1970 population	low 20,000's	low 20,000's
Population change 1960-70, %	17.0	16.3
Median family income	$13,434	$12,281
Median school years	12.7	12.5
Black, %	0.4	0.7
Foreign born, %	6.0	5.7
Water sodium level (1976), mg/l.	108 mg/l.	8 mg/l.

[a] 1970 U. S. Census Data.

existed for the past 7 years.

About 70% of the tenth grade class in the two cooperating public high schools returned parental permission slips and participated in the study. Thus, 300 white high school tenth graders from each community were screened. After spending at least 6 min seated, filling out a questionnaire, each student passed through three stations, with a measurement of casual, seated BP being taken at each station. These three measurements were averaged to estimate the blood pressure of each individual. The aneroid manometers were standardized twice a day. Approximately 150 students were screened each of 4 days.

The same four nurses took the BP in both schools. These nurses had been selected out of a larger pool on the basis of interobserver and intra-observer reliability. They were subsequently standardized against a highly trained observer who had recently been carefully standardized for a national BP study.

Results

Figure 4 illustrates the distribution of systolic and diastolic blood pressure in the two communities. There is a clear upward shift of 5 mm Hg in the systolic blood pressure distribution of females in the high sodium community. This upshift is essentially along the entire curve not just the upper end. Similar differences of 5 mm Hg in the curves exist for diastolic BP for females. For male systolic BP, the mean difference is 3 mm Hg and for male diastolic
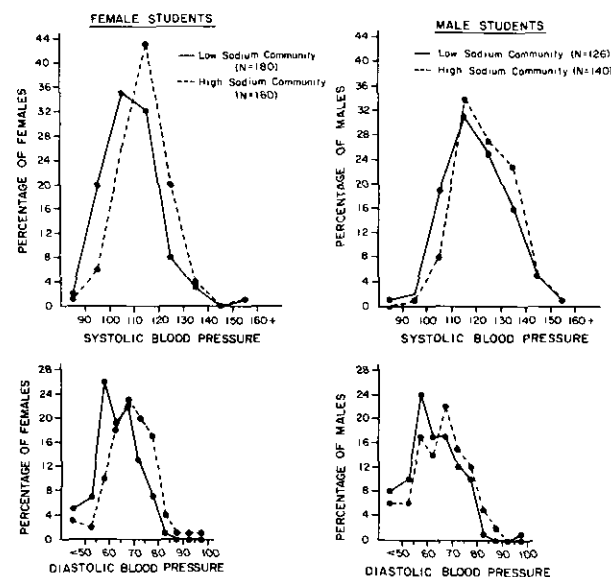

Figure 4. Systolic and diastolic blood pressure distributions by sex for sophomore high school students from high- and low-sodium communities.

	Tenth-grade students			Third-grade students		
	N	Mean systolic, mm Hg	Mean diastolic, mm Hg	N	Mean systolic, mm Hg	Mean diastolic, mm Hg
High sodium male	140	123.11	65.17	181	101.30	55.53
Low sodium male	126	119.54	62.48	145	98.03	52.42
Difference		3.57	2.69		3.27	3.11
High sodium female	160	113.49	67.80	165	97.94	57.05
Low sodium female	180	108.38	62.69	117	95.34	53.41
Difference		5.11	5.11		2.60	3.64

BP, 3 mm Hg. These differences were clinically as well as statistically significant and suggest that high sodium levels in drinking water may enhance premature aging, with respect to BP, in the exposed populations.

The study was later replicated with third grade students in the same two communities. The BP curves showed a similar upshift for third grade males as for the tenth grade males but not as large an upshift for the third grade females as for the tenth grade females. Table 2 compares the average upshift of BP for the tenth and third graders by sex. The differences in mean BP are similar in three of the age–sex groupings for both systolic and diastolic BP. Only the tenth grade females for both systolic and diastolic BP display a greater difference than the others. A possible explanation may be the fact that at age 15 a much greater proportion of females than males is sexually mature. Thus, the larger difference in BP for tenth grade females may represent a greater effect of the sodium on BP upon reaching physiological maturation.

In order to examine the differences in the water of the two communities, water samples from the homes of 100 children from each community were initially examined for nine metals thought to be related to BP: namely, sodium, cadmium, calcium, vanadium, lithium, lead, barium, copper, and zinc. Copper and zinc did explain some difference in BP of the two communities initially, but after controlling for the difference in sodium their contribution disappeared. However, the sodium effect, when controlled for copper and zinc, clearly remained although it was reduced somewhat. Additional home water samples are currently being examined for 40 elements.

Sodium and potassium excretion in the urine were not measured among the sophomores. Most of the intake of these electrolytes is excreted in the urine (7/). The data in this regard have recently been obtained for the third graders and is illustrated in the remaining figures. The values are not expressed in terms of total amounts of the electrolytes

excreted in the first morning urine per unit of body weight due to the difficulty in determining total volume of the samples. However, examination of the mean weight of the two third grade groups studied indicates the low sodium group to be slightly heavier (64.6 lb) than the high sodium group (63.1 lb). Figure 5 depicts levels in the first morning urine specimens of a random sample of the third grade students in the two communities. There is a clear upshift in sodium excretion levels in the high sodium community. Conversely, Figure 6 indicates a downshift in urine potassium levels in the high sodium community. Finally, Figure 7 illustrates the sodium/potassium ratio in the two groups. There is clearly some upshift in the ratio and particularly an excess at the highest levels in the high sodium community. These data support the hypothesis of excess sodium in the high sodium community as a possible causative factor in the blood pressure up-
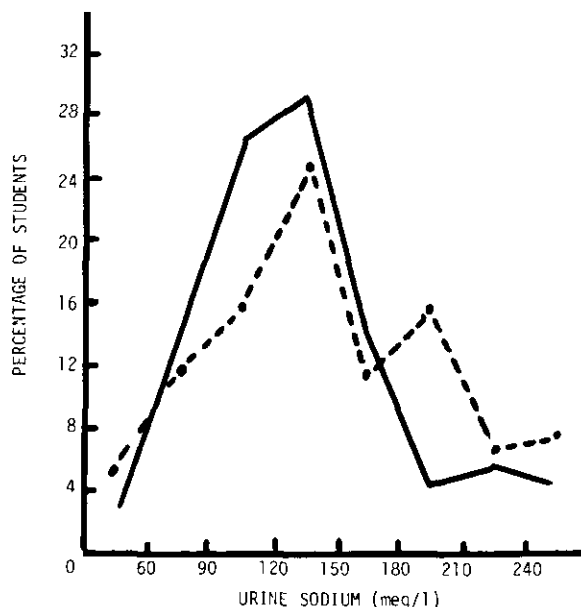

FIGURE 5. Sodium levels in first morning urine samples in third-grade students: (--) high sodium community ($n = 75$); (———) low-sodium community ($n = 72$).
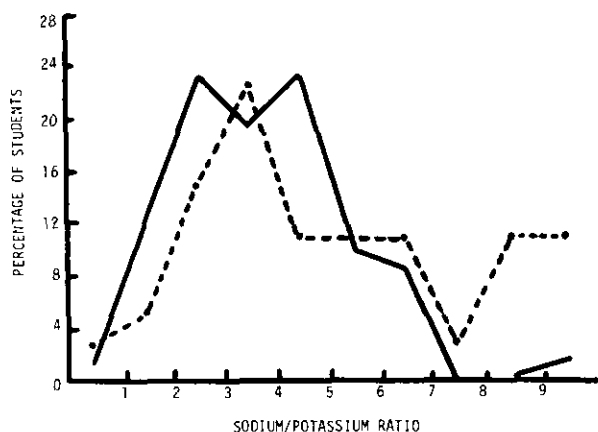
FIGURE 6. Potassium levels in first morning urine samples in third-grade students: (--) high-sodium community (*n* = 75); (——) low-sodium community (*n* = 72).
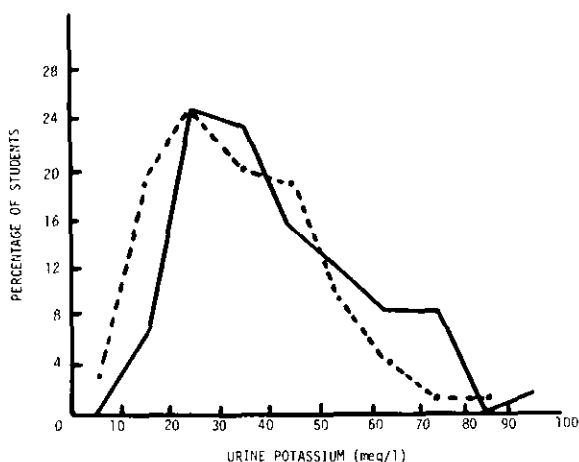

FIGURE 7. Sodium/potassium ratios in first morning urine samples in third-grade students: (--) high-sodium community (*n* = 75); (——) low-sodium community (*n* = 72).

shift. There has not yet been an opportunity to analyze the data further to assess the relationship between sodium/potassium ratio and blood pressure on an individual level.

Even though the two communities are so well matched in factors affecting BP, there is still the possibility that the differences in BP distributions are related to differences in dietary intake of sodium rather than a difference in water sodium levels. Detailed 24-hr diet histories from the third graders are being scored for sodium and potassium intake so that the relative contribution of dietary sodium and water sodium can be assessed. Assuming the consumption of 1.5–3 l. of water a day, up to 10% of daily sodium intake may be derived from water when that water contains 100 mg/l. of sodium (*7l*).

In summary, the person at high risk for hyperten-

sion appears to have a hereditary predisposition to a rise in BP in the presence of a high sodium intake. Actually, the degree of rise in BP may be an interaction between the amount of genetic predisposition and the level of sodium and its relation to potassium intake. As a person ages, the body, in an attempt to maintain homeostasis in the face of excess sodium intake, maladapts by increasing BP to reduce ECF. Our recent work in two Massachusetts communities supports the hypothesized effects of sodium on blood pressure.

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