/CALCIUM AND HYPERTENSION/

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CALCIUM AND HYPERTENSION

I. Introduction

Hypertension is defined as "elevation of the arterial blood pressure above the normal range expected in a particular age group" (1). The condition may be of unknown origin (essential hypertension), or the result of detectable organic causes (secondary hypertension), such as renal disease (renal hypertension), or diseases of the central nervous, endocrine, and vascular systems (2). Essential hypertension accounts for over 95% of cases in the U.S. (3). The World Health Organization has defined hypertension as arterial blood pressure of $\geq$160 mmHg systolic and/or $\geq$95 mmHg diastolic. Normal blood pressure is defined as <140 mmHg systolic and <90 mmHg diastolic. Intermediate values are classified as "borderline" hypertension (4).

Hypertension affects from 10 to 20% of the population of most industrialized countries. It greatly increases the risks of stroke, heart attack, and kidney and heart failure. For these reasons, and because it is almost without symptoms, it is known as "the silent killer" (5).

Approximately 25 million people in the U.S. are affected by this condition. The incidence in females is approximately 25% higher than in males, and about 60% higher in blacks than in whites. Incidence of hypertension increases with age, from less than 1/10th of 1% in persons under 17 years of age, to about 5% for ages 17-44 years, 24% for ages 45-64 years, and 38% for ages 65 years and over (6). The rate of hypertension has gone down in recent years. During the period 1971-1975, there were approximately 177 hypertensives per 1000 population. In the period

1976-1980, the rate decreased to about 145 cases per 1000 (6). The reason for this decline is not known. Hardy and Hawkins (7) and Kaplan (8) suggested that more intensive and better overall medical care is an important factor in this decline. Hypertension continues, nevertheless, to be a major health problem in the United States. The purpose of this report is to review the roles of selected nutrients on blood pressure regulation and hypertension, with specific emphasis on calcium.

II. Nutrients Involved in Blood Pressure Regulation

A number of nutrients may play a role in blood pressure regulation. Table 1 (3) shows the quality of data linking each nutrient with blood pressure regulation, and the proposed effect each nutrient has on blood pressure.

Table 1. Nutrient and Blood Pressure Data Inventory

Nutrient	Epidemiology		Animal Intervention		In Vitro	Human Intervention		Biochem-ical
	Intersocietal	Intrasocietal	Restriction	Supplementation		Restriction	Supplementation	
Protein	1•	1X	1.	1•	2•	0	0	0
Saturated fat	0	1•	1•	1.	0	1.	1•	0
Unsaturated fat	0	1.	1.	1•	0	0	1.	0
Simple cholesterol	0	0	0	0	0	2.	2•	1
Complex cholesterol	0	1.	0	0	0	0	1.	0
Na^+	2•	2—	1—	2X•	2•	1—	1X•	2
K^+	2.	2.	2.	2.	2.	0	1.	2
Ca^{2+}	1X.	1.	2•	2.	3.	0	1.	2
Mg^{2+}	0	1.	0	0	2.	0	0	1
Cl^-	0	0	1.	1•	1.	0	1•	1
PO_4	0	0	0	0	0	0	0	1
Cu^{2+}	0	0	0	0	1.	0	0	0
Pb^{2+}	0	1•	0	1•	0	0	0	1
VN^{2+}	0	0	0	1•	1•	0	0	0
MN^{2+}	0	1.	0	0	1.	0	0	0
Vitamins	0	1—	0	0	0	0	0	0
Alcohol	1•	2—	0	1—	1•	1.	1•	0
Total calories	2•	2•	1.	1•	0	1.	1•	0

• Data quality: none, 1 limited, 2 adequate. Blood pressure effect: • increase, X no effect, — decrease.

(Data from reference 3)

Sodium has received by far the greatest amount of attention in this area, while little has been given to the other nutrients. The data base relating the other nutrients to blood pressure regulation is, therefore,

quite incomplete. This failure in adequately assessing the roles of other nutrients may account, in part, for the inability thus far to conclusively link sodium to the development of human hypertension (3). Some of the nutrients which exhibit the strongest evidence for having a role in blood pressure regulation will be discussed here briefly. Calcium will be discussed in the next section.

A. Sodium

Porter (9) has reviewed the sodium hypothesis in hypertension. He noted that, in 1904, dietary salt restriction was associated with a decline in blood pressure in hypertensive patients. A number of epidemiologic studies, covering approximately 50 years, have shown a positive correlation between salt intake and hypertension rates. One study showed no correlation.

Up to the 1940s, the chloride ion, rather than the sodium ion, was thought to be the factor in salt which led to abnormally high blood pressure. In 1945, however, Grollman [as reviewed by Porter (9)] showed that sodium restriction brought about a decrease in blood pressure. Three years later, other researchers confirmed an abnormal sodium retention by certain hypertensives.

The antihypertensive effect of diuretics was reported in two studies in 1959 (9). In both cases, the authors concluded that the diuretic-induced decrease in extracellular fluid volume was responsible for the decrease in blood pressure. The diuretic used in both of these trials was chlorothiazide which decreases renal sodium reabsorption, thus increasing its net excretion and increasing water excretion as well (10).

Porter (9), and also McCarron (3), noted several clinical studies showing a positive correlation between sodium intake and hypertension.

In 1982, MacGregor et al. (11) reported a double-blind randomized cross-over trial of mild sodium restriction in essential hypertension. A significant decrease in blood pressure was obtained with declining sodium intake, whereas a subsequent increase in sodium intake caused blood pressure to again elevate.

Sodium's proposed role in hypertension suggests a renal dysfunction leading to an inability to adequately excrete sodium. Such inability would lead to an abnormal retention of sodium, which, through osmosis, would cause an increase in extracellular fluid volume. This would imply an increase in blood volume, and hence, blood pressure, according to Porter (9).

Porter (9) noted that in 1976, researchers Haddy and Overbeck (12) proposed that abnormal sodium retention and subsequent extracellular fluid expansion and hypertension were mediated humorally. A "natriuretic hormone" is secreted in response to pathologic sodium retention (13). It would act, via cellular ATP-ase activity, to increase sodium content of vascular smooth muscle cells. This influx of sodium would decrease the concentration gradient of extracellular sodium to intracellular sodium, bringing about an influx of calcium ions into the cell (14), and with this, an increase in vascular tension. Thus, this hormone would bring an increase in blood pressure in an attempt to increase renal excretion of excess sodium.

Sodium's proposed role in hypertension is backed by substantial data. However, some studies have shown no correlation between sodium intake and blood pressure (15,16), so that there is not yet a consensus among experts that dietary sodium restriction would be beneficial for all persons (9).

B. Potassium

Tannen (17) has reviewed the role of postassium in blood pressure regulation and in hypertension, in particular. Most studies have shown that potassium depletion has a hypotensive effect in normotensive animals and in hypertensive animals and humans. This effect may be brought about by a decrease in aldosterone levels without which sodium reabsorption would be decreased, or a decrease in vasopressin release. Also, a decrease in responsiveness to the pressor effects of angiotensin II may be responsible, which, in turn, might be due to a potassium depletion-induced decrease in membrane receptor affinity to angiotensin II.

Conversely, a high potassium intake also is associated with a lowering of blood pressure in hypertensive animals and humans, but has no effect in those with normal blood pressure. Possible modes of action for this effect include natriuresis with sodium depletion, decreased plasma renin activity, and an alteration in neurologic components of blood pressure control. These hypotheses have been studied, but the exact role potassium plays in blood pressure control still is not known.

C. Magnesium

Magnesium is an essential element in normal cardiovascular function. It functions both via membrane-associated actions, such as stabilization of calcium channels, and in the cytosol, catalyzing the actin-myosin-calcium interaction, which ultimately determines vascular tone (18). However, the element's potential role in hypertension is not clearly understood, and contradictory reports exist as to its possible therapeutic effect on this condition (19).

D. Protein

Dietary protein content seems to have little effect on systemic blood pressure (20). However, a high intake appears to contribute to renal hypertension. It does this by increasing the glomerular filtration rate, thus increasing the glomerular capillary pressure and plasma flow rate.

E. Lipids

Smith-Barbaro and Paucak (21) reported a number of studies showing a blood pressure lowering effect in hypertensive animals and humans by increasing the proportion of polyunsaturates to saturated fats in the diet. The mechanisms for this effect are not known, though it is suspected that prostaglandins may be involved.

III. Calcium and Blood Pressure Regulation

Calcium is a critical factor in the regulation of cardiovascular physiology. It is an essential component, via both membrane-associated and cytosolic-related mechanisms, in the function of vascular smooth muscle cells (22).

The study of calcium's role in blood pressure regulation was undertaken after a number of epidemiologic studies (23-26), beginning in 1960 (23), showed a negative correlation between cardiovascular mortality rates and water hardness. Many studies, especially in recent years, have shown that calcium does play an important part in blood pressure control.

Intracellular calcium acts as a determinant of cardiovascular muscle contraction (22). It acts via the central nervous system to integrate the various components of blood pressure control, and renally to modify water and solute excretion by affecting the filtration rate and reabsorption processes (18). Calcium's most prominent contribution to blood pressure

regulation, however, is its influence on vascular resistance. Membrane receptor binding is dependent on calcium. Calcium also integrates the membrane fluxes of sodium and potassium, thus influencing their actions on blood pressure control (18). Probably an increased influx of calcium into vascular smooth muscle cells gives rise to increased binding of calcium to calmodulin, a small intracellular protein, which would then initiate a series of biochemical events resulting in actin-myosin interaction and smooth muscle contraction (27). The exact role of calcium in blood pressure control is, however, like those of the other nutrients discussed, incompletely understood at this time.

Adequate dietary levels of this cation seems to have a protective effect against both experimental and human hypertension according to a number of studies (15,16,28,29). Some studies comparing serum calcium levels in hypertensives and normotensives, however, have found no differences between these groups (30-33).

IV. The Evidence

A. Water Hardness and Cardiovascular Disease

The initial evidence associating calcium with hypertension and cardiovascular disease came from reports of an inverse relationship between water hardness and cardiovascular mortality rates (23-26,34-37). Schroeder (23,24) looked at cardiovascular death rates and water hardness in American cities and found highly significant negative correlations between these factors for both men and women. Hypertensive deaths, specifically, also were significantly negatively correlated to water hardness. Crawford et al. (34) looked at 61 towns in England and Wales. A highly significant negative correlation was found there also. Cardiovascular death rates were approximately 50% higher in soft water than in

hard water areas (34). In 1971, Stocks (35) found significant negative correlations between water hardness and hypertensive and chronic rheumatic heart disease in 80 towns in England and Wales. In the 100 largest U.S. cities, Voors (36), compared coronary heart disease deaths with water calcium content. A significant negative correlation was found for whites, but not for blacks.

In 1973, Stitt et al. (25), using the data obtained by Crawford et al. (34), sampled six towns from each of the hard and soft water categories. Only men, aged 40-65 years, and matched for social class, occupation, and general way of life, were studied. Diastolic blood pressure, but not systolic, was significantly lower in the hard water areas, though the difference was not large. In a study analyzing the association of individual elements in the water with cardiovascular disease in South Wales, Elwood et al. (37) found significant negative correlations for three elements (magnesium, calcium, and potassium). That for calcium was the greatest. Schroeder and Kraemer (38) found in 94 major U.S. cities a small, but significant, negative relationship for women, but not for men, between death rates from hypertensive heart disease and water calcium content.

The studies discussed above all dealt with industrialized societies. In 1976, Masironi et al. (26), reported a study of a more primitive society in New Guinea. Fifteen villages along a certain river were analyzed for a correlation between blood pressure and the calcium content of the river water, which the villagers used for drinking. A significant negative correlation was found. Even in the low calcium areas, however, the average blood pressures did not approach the hypertensive level. They were, in mmHg, 115.8/75.1 for men, and 117.5/74.7 for women, as

compared to 104.5/67.4 and 108.9/70.7, respectively, in the high calcium areas.

Not all studies, however, have shown associations between water hardness and cardiovascular disease rates. Elwood et al. (39) found no correlation between blood pressure and water hardness. Dawson et al. (40) studied 24 county seats in Texas and found no correlation between coronary heart disease or stroke and calcium or magnesium levels of the drinking water. One finding of interest there, however, was that the ratios of sodium to calcium and sodium to magnesium were both significantly positively correlated with death rates from those diseases. They suggested that calcium and magnesium may have a protective effect against cardiovascular disease, possibly by competing with sodium for transport in the intestinal lumen, thereby increasing sodium excretion.

Most of the studies comparing water hardness and cardiovascular disease suggested a protective effect from hard water. Such studies cannot, however, prove this to be a cause-effect relationship (3). The major objection usually raised to water hardness-cardiovascular disease studies in industrialized societies is that many other factors may be involved, such as degree of industrialization, socioeconomic environments, treatment and artificial softening of drinking water, smoking, and food choices, which also may affect cardiovascular disease rates (26). Masironi et al. (26) stated that in their study of a more primitive people in New Guinea, these variables were greatly reduced. Negative correlations were still found between water calcium content and blood pressure, which strengthens the conviction that this association was real. McCarron (22) suggested that although this association is controversial, one possibility is that the calcium added to the diet in hard water areas

may be sufficient to keep many persons above a critical threshold value of total intake that protects against the development of hypertension.

B. Dietary Calcium Intake and Blood Pressure

Another form of epidemiologic study which has shown an association between calcium and blood pressure is that surveying the dietary intake and blood pressure. McCarron et al. (3) analyzed the HANES I data (15) for such a correlation. Of the original 20,749 subjects, 12,409 adults aged 20-74 years were selected who had denied a history of hypertension, drug therapy, or chronic diseases requiring diet therapy. Four other nutrients, sodium, potassium, protein, and fat, which have been linked with cardiovascular disease, also were analyzed. Twenty-four hour dietary recall was used. The authors noted that such data are not predictive of any given person's lifetime intake but can accurately assess the nutrient profile of a population. Estimates of nutrient intake were made only from food and so did not include that coming from water. Hypertension in this study was defined as a blood pressure of 160/95 mmHg or greater.

Figure 1 (3) shows the systolic blood pressure as it increased with age in men and women as found in HANES I (15).

Figure 1. Systolic blood pressure profile of the United States 1971 to 1974 for men and women from HANES I data

(Data from reference 3)

Figure 2 (3) shows the intake of the five nutrients by hypertensives divided into three age groups and expressed as a percentage of the intake of normotensive subjects. This is shown on a per 1000 calorie basis rather than on total nutrient intake because the average calorie intakes of the two groups were not the same; that for hypertensives was 12% less than for normotensives.

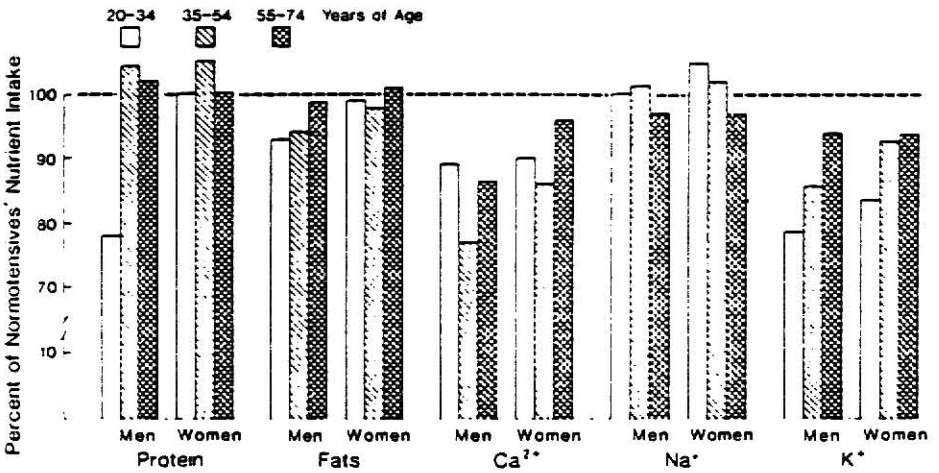

Figure 2. Consumption by hypertensive men and women, ages 20 to 34 years, 35 to 54 years, 55 to 74 years, of protein, fats, Ca^{2+}, Na^{+}, K^{+} recorded as densities (either grams or milligrams of the respective nutrients per 1000 kcal of food) and indexed as a percent of normotensive subjects' intake.

(Data from reference 3)

On the basis of total nutrient intake, hypertensives consumed less of all five nutrients than did normotensives. On a per 1000 calorie basis, however, only calcium and potassium showed significantly lower intakes by hypertensives. Of the five nutrients, calcium intake differed the greatest between hypertensives (572±17 mg) and normotensives (695±7 mg) ($p<0.0001$). Hypertensives consumed 18% less calcium than did normotensives. The reduced intake of potassium in hypertensives was also significant both in white and non-white subjects, but the reduction was

not as great as that for calcium. The reductions in the other nutrients, magnesium, protein, and fat, seemed simply to reflect the overall lower calorie consumption by the hypertensives.

In men, the differences in calcium intake were greater than in women. In the 35-54 year age group, white male hypertensives consumed 27% less calcium (688±61 mg) than normotensive white males (935±38 mg). Non-white males in this age group were almost four times as likely to be hypertensive as white males (4% whites; 15% non-whites). Here again the difference in calcium intake was considerable, 367±53 mg for non-white hypertensives and 634±48 mg for non-white normotensives (3). Figure 3 (3) shows the intakes of the five nutrients in white and non-white hypertensives expressed as a percentage of that for normotensives. Of the five

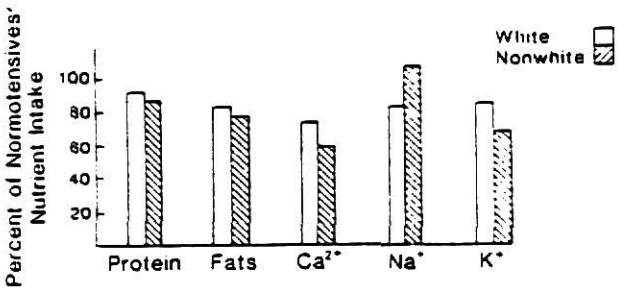

Figure 3. White and nonwhite male hypertensive subjects, ages 35 to 54 years, consumption of protein, fats, Ca^{2+}, Na^{+}, K^{+} indexed as a percent of normotensive subjects intake.

(Data from reference 3)

nutrients analyzed, calcium intake, and to a lesser extent potassium intake, corresponded with the demographic characteristics of hypertension. The authors stated that this evidence does not preclude a role for the other nutrients in the etiology of hypertension but suggests that their roles are probably more limited than those of calcium and potassium.

McCarron et al. (16) compared the calcium intake of 46 recently diagnosed essential hypertensives with that of 44 normotensive controls, matched for age, sex, and race. For estimation of calcium intake, 24-hour dietary recall was used. Hypertension was defined as a diastolic blood pressure of >95 mmHg or mean arterial pressure of >105 mmHg. None of the test subjects were using either medication or any special diet for hypertension. Figure 4 (16) compares the intakes of some nutrients for hypertensives with those of normotensives and with the average intakes for all subjects in the HANES I (15).

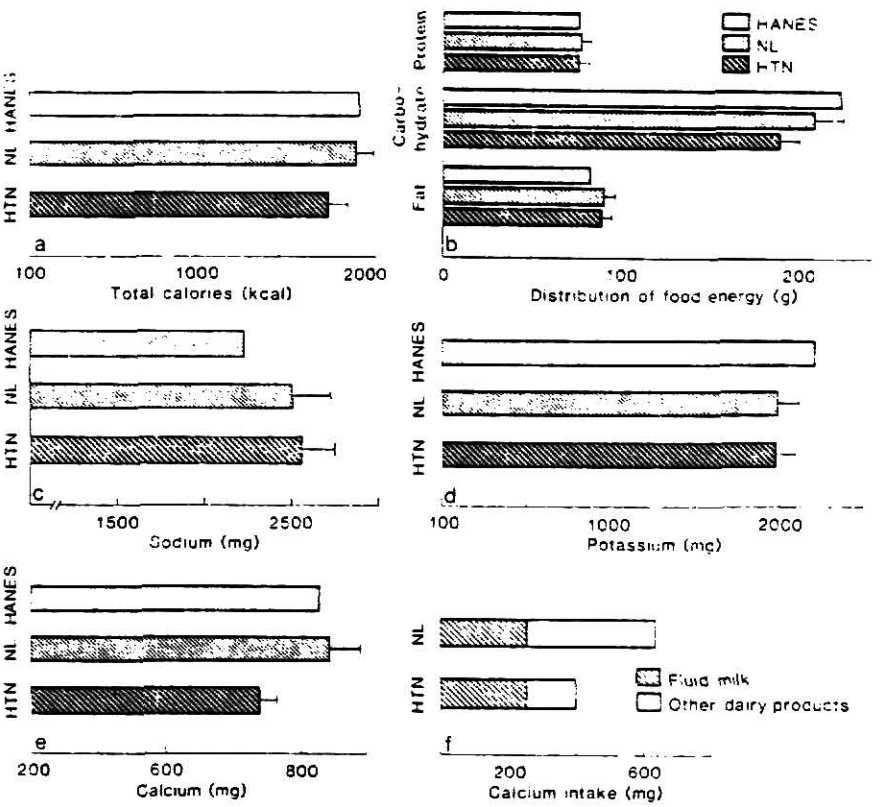

Fig. 4. Results of a pilot survey of the dietary calcium intake of 46 subjects with essential hypertension and 44 normotensive control subjects. The results are compared with the HANES data (15). (a) Reported dietary intake of total calories; (b) distribution of food energy; (c) sodium intake; (d) potassium intake; (e) calcium intake; (f) distribution of dairy calcium intake between fluid milk and other dairy product sources.

(Data from reference 16) NL = normotensives HTN = hypertensives

Total calorie intake for hypertensives was less by 8% than that for normotensives although this was not significant. Normotensives and hypertensives consumed approximately equal amounts of carbohydrate, protein, and fat. Sodium and potassium intakes were very similar for the two groups. Daily calcium intake, however, differed significantly ($p<0.05$). For normotensives, it was 886±89 mg, and for hypertensives, 668±55 mg. Additionally, out of the 46 hypertensives, only one reported a calcium intake of more than one gram per day. Of the 44 normotensives, 18 reported an intake of more than one gram of calcium per day. The sources of dietary calcium also differed between the two groups. Similar amounts were consumed from non-dairy sources and from fluid milk. However, the daily calcium intake from dairy products other than fluid milk amounted to 400±78 mg for normotensives and only 148±34 mg for hypertensives ($p<0.025$).

The authors suggested the possibility, based on these results, that individuals with hypertension may ingest less calcium than persons with normal blood pressure. They noted, however, that they did not investigate the possible influence of other dietary factors than those discussed, magnesium being one important omission. Possible influences of socioeconomic status also were not analyzed.

Still, the suggestion is that dietary calcium intake may be an important factor in influencing a person's likelihood of developing hypertension. Also the authors stated that, in view of the similar reported intakes for fat and sodium for both hypertensives and normotensives, the results should sound a note of caution. Foods high in these components are frequently also high in calcium, so that dietary recommendations for restricting cholesterol and sodium for hypertensives

may result in a concurrent, inadvertent additional reduction in calcium intake.

Ackley et al. (28) studied the calcium-blood pressure association to see if it was independent of age, obesity, and alcohol consumption. However, only calcium intake from dairy products was analyzed. Subjects consisted of 5,050 adult residents, aged 30-79 years, of a city in California. To the categories of hypertension and normotension, a third, borderline hypertension, was added. The definitions for these, in mmHg, were: normotension, <140 systolic and <90 diastolic; borderline hypertension, $\geq$140 but <160 systolic and $\geq$90 but <95 diastolic; and hypertension, $\geq$160 systolic and $\geq$95 diastolic. Further, hypertensives were divided into treated (those receiving treatment for their condition) and untreated (those not receiving treatment for hypertension) groups.

Reported whole milk consumption was significantly lower in older versus younger subjects, and it was lower in women than in men. In women, no significant differences were found between calcium intakes of hypertensives, borderlines, and normotensives. In consumption of dairy products, the only significant findings for women was a lower intake of whole milk by treated hypertensives as compared to that of normotensive women.

In men, both systolic and diastolic blood pressures decreased as calcium intake from dairy products increased. After adjustment for age, obesity, and alcohol consumption, however, a significant negative correlation was found only for diastolic blood pressure ($p<0.05$). The observation that systolic blood pressure was less well correlated with calcium intake from dairy products in men may, according to the authors, reflect either the greater variability of systolic blood pressure, or its

stronger association with age, obesity, or alcohol consumption. They suggested the failure to find a significant correlation in women may likely reflect a more complex relationship of covariates to blood pressure in women.

McCarron et al. (16) found non-milk dairy products highly negatively correlated with blood pressure, while milk alone was not. In contrast, Ackley et al. (28) showed the differences in calcium intake from dairy products among the different blood pressure groups to be most strongly correlated with milk consumption. The authors noted that non-dairy sources of calcium were not taken into account so that neither the quantity of this calcium nor its possible correlation with blood pressure could be analyzed. The authors also noted that some component of dairy products other than calcium may be responsible for the correlation observed. They suggested, however, that calcium is most likely the factor involved.

Morris et al. (29) compared the calcium intake of 39 hypertensives and 31 normotensives, using 24-hour dietary recall. Hypertension was defined as a mean arterial pressure of $\geq$105 mmHg. A significant difference ($p<0.01$) was found between the calcium intake of hypertensives (728±310 mg/day) and normotensives (939±338 mg/day).

Garcia-Palmieri et al. (41) studied calcium intake and blood pressure in 7,932 Puerto Rican men aged 45-64 years. Twenty-four hour dietary recall was used. Hypertension was defined as $\geq$160 mmHg systolic and $\geq$95 mmHg diastolic blood pressure. In contrast to two other studies (3,16), subjects on special diets were not excluded from analysis. The men were divided into urban and rural groups, and into two age groups, 45-54 years of age and 55-64 years of age.

Milk consumption averaged very close to 16 oz/day for each of the four groups, and ranged from none to more than 32 oz/day. Relatively small intakes of other dairy products were reported. On the average, milk provided slightly over 60% of all calcium intake, with peas and beans contributing the next largest amount (10%). Calcium intakes from non-dairy and non-milk dairy products were very similar in hypertensives and normotensives. However, individuals who consumed more milk had significantly lower blood pressures ($p<0.05$) in all groups except younger rural men. As in the study by Ackley et al. (28), this contrasts with McCarron et al. (16), who found blood pressure more strongly associated with consumption of non-milk dairy products than with milk. The relationship was strongest in younger urban men, where 20% of those who consumed no milk were hypertensive, compared to only 4% of those consuming four or more glasses of milk per day. Also, the negative association of milk consumption with blood pressure was stronger in dark-skinned than in light-skinned men.

Significant correlations with blood pressure also were found for other factors, including blood glucose, relative weight, and heart rate (41). These were all positive. When they were controlled for, however, the negative association of milk consumption with blood pressure persisted. The variables of protein, fat, and carbohydrate had low correlations with blood pressure. Sodium was not discussed.

The authors (41) noted that they could not be certain that the association found between milk consumption and blood pressure indicated a true relationship or only a poorly measured one. Multiple 24-hour dietary recalls would have characterized the usual diets of the subjects better than single recalls as was done. The authors seemed somewhat less

confident in this method than did McCarron (3). They noted further that if the association was real, it could be due to some other covariable of milk, rather than calcium, or that there could be cultural or social factors associated with milk consumption which might affect blood pressure. They suggested that if calcium is the factor involved, increasing whole milk consumption may not be the answer because of the probable concurrent increase in saturated fat in the diet. More research is called for to define the risks and benefits of any recommended dietary changes.

C. Urinary Calcium and Blood Pressure

McCarron et al. (30) appears to have been the first to compare the urinary calcium excretion of hypertensives and normotensives. This was done in an attempt to explain the higher incidence of hyperparathyroidism in hypertensives as compared to normotensives. Subjects were 34 hypertensives (mean arterial pressure >105 mmHg and/or >95 mmHg diastolic blood pressure) and a normotensive control group matched for age and sex.

Total serum calcium was not different between the two groups (9.5±0.1 mg/dl for both), though parathyroid hormone (PTH) was significantly higher ($p<0.025$) in the hypertensives (79±3.1 mEq/l for hypertensives, 67±3.3 mEq/l for normotensives). Still, however, this level was not beyond the normal range for PTH. Serum ionized calcium was not analyzed separately from total serum calcium.

Calcium excretion was directly correlated with sodium excretion in both hypertensives and normotensives. The hypertensives, however, had significantly more ($p<0.05$) calcium in their urine for any level of sodium excreted. Figure 5 (30) plots the urinary calcium excretion against urinary sodium excretion for the two groups. For any given sodium

excretion, hypertensives excreted from 1.4 to 3.6 times as much calcium as did normotensives.

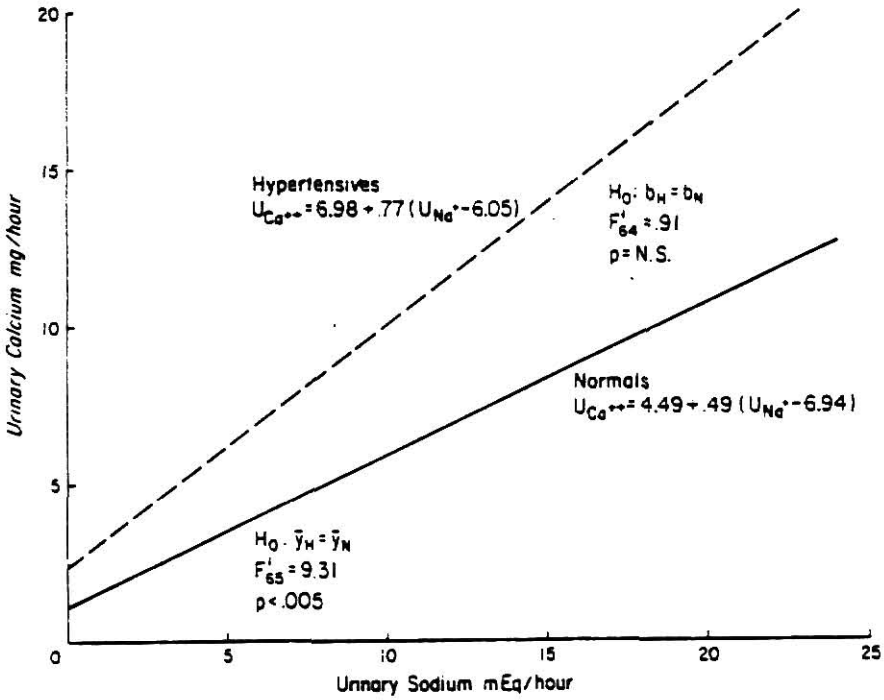

FIGURE 5. *Comparison of equations relating U_{Na+} to U_{Ca++} for normal and hypertensive subjects.*

(Data from reference 30)

The authors suggested that basal parathyroid function is enhanced in hypertensives and is probably due to a previously unrecognized relative hypercalciuria. They suggested also that this increased parathyroid function is an appropriate homeostatic response to the hypercalciuria in an attempt to keep serum calcium at the correct level. The renal handling of calcium is influenced by many factors, the most important being renal sodium excretion. Throughout the proximal portions of the nephron these two cations are handled identically. In the distal tubules, however, they are not. Here is where the final adjustments of calcium excretion occur,

and this is also the point at which PTH stimulates calcium reabsorption (30). The authors suggested that the defect in hypertensives renal calcium excretion is therefore probably in the distal tubules (30).

Kesteloot and Geboers (42) reported a study of 3,541 men in the Belgian army. Significant positive correlations were found between urinary calcium excretion and both systolic and diastolic blood pressures ($p<0.05$). No underlying cause for this effect was suggested.

In a study of urinary calcium excretion and blood pressure in 688 Belgian inhabitants, Staessen et al. (43) found a significant positive correlation in adult men. The study involved subjects of both sexes 10 years of age and older. In all youths (10-19 years), significant positive correlations were found between urinary calcium output and both systolic and diastolic blood pressure. However, after adjusting for body weight and pulse rate, the significance disappeared. In adults of both sexes, a significant positive correlation was found between urinary calcium and diastolic blood pressure before adjusting for age and body weight. After these adjustments, significance remained only for men ($p=0.04$). Diastolic blood pressure in the men ranged from 45-105 mmHg, while urinary calcium excretion ranged from 0.7 to 12.5 mmol/24 hours. Three other urinary electrolytes, sodium, magnesium, and potassium also were analyzed. Neither sodium nor magnesium showed a correlation with blood pressure. For potassium, however, a significant negative correlation was found with both systolic ($p<0.001$) and diastolic ($p<0.01$) blood pressures in adult men. After correction for potassium as well, calcium's significance remained.

Strazzulo et al. (31) analyzed urinary calcium excretion in 55 hypertensives (diastolic blood pressure >95 mmHg) and 55 normotensives in Italy. Each group consisted of 28 men and 27 women, mean ages 42.7±1.1

years for hypertensives and 40.3±0.6 years for normotensives. The hypertensives were diagnosed as having essential hypertension and none had been on medication or any special diet for at least one month.

Urinary calcium excretion was significantly higher in both hypertensive men and women. Urinary calcium values per 24 hours were: for male hypertensives and normotensives, 4.75±0.8 and 3.77±0.3 mmol/l, respectively ($p<0.03$) and for female hypertensives and normotensives, 4.43±0.3 and 3.39±0.3 mmol/l, respectively ($p<0.02$). As in the study by McCarron et al. (30), sodium excretion was directly related to calcium excretion in both patients and controls. The ratio of calcium to sodium excretion was significantly higher in hypertensives than in normotensives, with an average 20% increase in calcium excretion for any given level of urinary sodium. Serum total and ionized calcium concentrations were slightly but not significantly higher in normotensives. Plasma PTH was significantly higher in hypertensives (2.78±0.19 vs 2.20±0.08 m-i.u./ml for normotensives) ($p<0.05$).

In a subsample of seven men from each group, a more detailed investigation of renal calcium handling was made. An intravenous calcium load was given at the rate of 15 mg calcium/kg body weight infused over a three hour period. Figure 6 (31) plots the urinary and serum ionized calcium concentrations for these 14 men. Regression slopes were significantly different in the two groups. Hypertensive men excreted significantly more calcium in their urine for any level of serum ionized calcium.

The authors mentioned three possible metabolic disorders which conceivably could account for the hypercalciuria found in the hypertensives. These included increased bone resorption, increased intestinal calcium absorption, and a primary renal defect in calcium handling. Increased

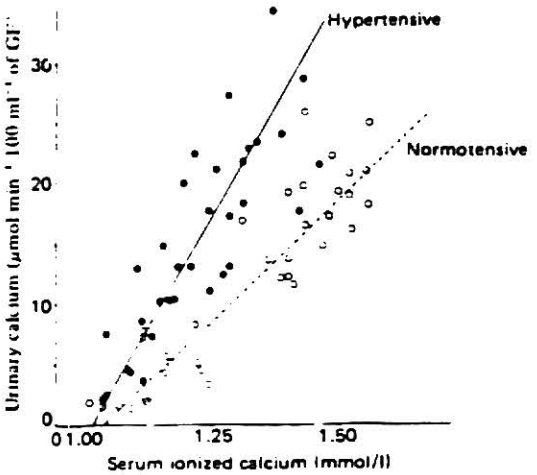

FIG. 6. Comparison of urinary calcium excretion rates in normotensive (○: $n = 7$ male) and hypertensive (●: $n = 7$ male) subjects during intravenous calcium infusion. A regression equation of urinary calcium excretion on serum ionized calcium concentration was set up for each subject. The individual a and b coefficients were averaged to obtain the regression lines of the normotensive ($y = -49.81 + 46.51x$) and the hypertensive ($y = -77.45 + 75.58x$) group respectively.

(Data from reference 31)

bone resorption was considered unlikely as it is associated with decreased PTH levels and enhanced serum calcium concentrations, neither of which was found here. Increased intestinal calcium absorption was evaluated by measuring calcium excretion in the fasting state, which would not be affected by variations in dietary calcium intake. Hypertensives in this state excreted approximately twice the amount of calcium as did normotensives. A primary renal defect in calcium handling was suggested as the most likely explanation for the observed hypercalciuria in the hypertensive subjects. This is in agreement with McCarron et al. (30). The renal defect suggested is somewhat different from that suggested by McCarron et al. (30). The proximal tubule, rather than the distal tubule of the nephron, is suggested to be the site of the defect. A failure to reabsorb sufficient calcium might be a stimulus to increase PTH secretion in an attempt to increase calcium reabsorption in the distal tubule, accounting for the increased PTH levels found in the hypertensives.

Morris et al. (29) carried out a randomized placebo-controlled study of urinary calcium excretion in 39 hypertensives (mean arterial pressure $\geq$105 mmHg) and 31 normotensives. The subjects were treated for eight weeks with either a one gram calcium supplement or a placebo. In the

24-hour dietary recall before treatment began, hypertensives reported a calcium intake of 22% less than that of normotensives. For both groups, urinary excretion of sodium, potassium, magnesium, and phosphate were similar at baseline and did not vary significantly with either treatment. Urinary calcium excretion, however, was 63% greater at baseline for hypertensives (207±140 vs 127±86 mg/dl for normotensives) ($p<0.01$). Placebo treatment did not modify this difference. Treatment with the one-gram calcium supplement, however, increased urinary calcium excretion in normotensives (214±118 mg/dl) ($p<0.05$), but did not change that in hypertensives. The authors suggested that there is a primary difference in the calcium homeostatic mechanisms of hypertensives which may contribute to their developing states of relative calcium depletion.

D. Serum Calcium and Blood Pressure

Serum levels of calcium in hypertensives and normotensives have been the subject of conflicting reports. Some studies have shown no correlation of serum total calcium with blood pressure (30,31,44) while others have shown a positive correlation (42,45,46). Serum ionized calcium has been found to have no correlation (31), a negative correlation (44), and a positive correlation with blood pressure (47). In addition Resnick et al. (19) found low serum ionized calcium in low-renin hypertensives and high serum ionized calcium in patients with high-renin hypertension.

McCarron et al. (30) found no correlation of total serum calcium with blood pressure in 34 hypertensives (mean age 44.6 years) and 34 normotensives (mean age 44.9 years). The mean serum total calcium concentration was, in fact, identical in the two groups (9.5±0.1 mg/dl). Strazzullo et al. (31) also found no correlation of total serum calcium with blood

pressure. Serum ionized calcium also was not significantly different in the two groups (1.09±0.01 vs 1.10±0.01 mmol/l for hypertensives and normotensives, respectively). McCarron (44) studied total and ionized calcium in 23 hypertensive and 23 normotensive controls matched for age, sex, and race. Total serum calcium was nearly identical in the two groups (4.7±0.48 mEq/l for hypertensives and 4.78±0.29 mEq/l for normotensives). Serum ionized calcium, however, was significantly lower ($p<0.001$) in hypertensive subjects (2.07±0.07 mEq/l for hypertensives vs 2.17±0.03 mEq/l for normotensives), though both values are within the normal range given by Richards et al. (2.0-2.4 mEq/l) (48). The author suggested the probable cause of this relatively reduced serum ionized calcium in hypertensives was an abnormally enhanced binding of calcium to extracellular proteins. He suggested that the total serum calcium does not change, but that a greater than normal proportion of it is protein-bound, leaving less in the ionized form.

On the other hand, Kesteloot and Geboers (42), in their study of Belgian army personnel noted above, found a highly significant positive correlation of total serum calcium with both systolic and diastolic blood pressure in men ($p<0.001$). A distinction was not made between hypertensive and normotensive groups. In women, a significant relationship was not found. Serum ionized calcium was not measured. The authors stated that in a population with normal total serum protein and normal serum pH, ionized serum calcium will be a constant function of total serum calcium. Serum pH, however, was not measured. Only one serum protein, serum gamma-glutamyl transpeptidase, was measured, and it was significantly positively correlated with blood pressure. No conclusions can, therefore,

be drawn as to what the level of serum ionized calcium may have been in the subjects.

Bulpitt et al. (45) examined 357 men and 341 women and found a significant positive correlation of total serum calcium with systolic but not with diastolic blood pressure. Hawthorne et al. (46) compared total serum calcium in 133 hypertensives (63 men and 70 women) aged 45 to 64 years and 103 controls (52 men and 51 women). Hypertensives had slightly, but significantly, higher levels of total serum calcium (2.41 vs 2.33 mmol/l for normotensives) ($p<0.001$). When total serum calcium was corrected for serum albumin, the trend persisted ($p<0.02$). Frankly high serum calcium (>2.6 mmol/l) was found in 8.3% of hypertensives and 1% of normotensives. No significant correlations were found specifically between total serum calcium and either systolic or diastolic blood pressure, in contrast to Kesteloot and Geboers (42) and Bulpitt et al. (45) findings.

In a study of a sex-dependent relation between serum ionized calcium and blood pressure, Fogh-Anderson et al. (47) analyzed 977 45-year-olds (465 men and 512 women) in Denmark. Subjects were fasted before blood was drawn so as to eliminate variations of diet from affecting serum ionized calcium. Subjects taking medication were included. This, however, did not affect overall results. On the average, men had both higher blood pressures (121.8/75.5 mmHg) and higher levels of serum ionized calcium (1.23 mmol/l) than did women (112.7/69.8 mmHg and 1.20 mmol/l, respectively). Serum ionized calcium concentrations in the whole epidemiologic sample were positively correlated with both systolic and diastolic blood pressure ($p<0.001$). When the sexes were analyzed separately, however, only a weak positive correlation ($p<0.05$) was found for systolic blood pressure in men, and no significant correlation was found in women.

Twenty women and 50 men were categorized as hypertensive (systolic >140 mmHg or diastolic >90 mmHg). The average levels of serum ionized calcium in these subjects were normal (1.19 and 1.23 mmol/l for hypertensive women and men, respectively). Thirty-seven women were postmenopausal. Thirteen of these were taking estrogens and had normal serum ionized calcium (1.20 mmol/l). The 24 who were not taking estrogens had increased serum ionized calcium (1.21 mmol/l) ($p<0.01$). This was in agreement with Belizan and Villar (49) who stated that estrogens decrease calcium levels by causing diminished calcium reabsorption. No significant differences in blood pressure were observed between the pre- and postmenopausal women.

Resnick et al. (19) compared serum ionized calcium and magnesium concentrations with renin activity in 98 hypertensives (blood pressure $\geq$150/95 mmHg) and 102 controls. Blood was drawn in the fasting state. Hypertensives were divided into three subgroups according to their levels of renin activity. They were categorized as having low-renin, normal-renin, or high-renin hypertension.

Serum magnesium varied inversely and significantly with renin activity. Serum ionized calcium varied directly and significantly with renin activity. Values were 2.20, 2.09, 2.24, and 2.34 mEq/l for normotensives, low-, normal-, and high-renin hypertensives, respectively. Low-renin hypertensives had significantly less serum ionized calcium than did normal- or high-renin hypertensives or normotensive controls. High-renin hypertensives had significantly higher serum ionized calcium than did all other groups. Normal-renin hypertensives did not differ in serum ionized calcium concentration from normotensive controls. In spite of the differences found, the vast majority of serum ionized calcium levels among

all hypertensives were within the same normal range as that found in normotensive controls.

A finding of importance in this study was that if all the hypertensives had been analyzed together without regard to renin activity, the differences in ionized calcium between the various hypertensive subgroups would have cancelled each other out, and no significant differences would have been found in serum ionized calcium levels between hypertensives and normotensive controls. The authors suggested that in this context, the low serum ionized calcium found in hypertensives by McCarron (44) may reflect a predominance of low-renin hypertensives in the study population. They proposed that the low serum ionized calcium levels found in low-renin hypertensives reflect increased levels of intracellular ionized calcium, which would account for the increased vasoconstriction. This increased intracellular calcium also would decrease renin and parathyroid hormone (PTH) secretion, which would be compatible with lower levels of serum ionized calcium. The question then arises as to the cause of the increased intracellular calcium in the first place. Various abnormalities of different membrane ion pumps, including sodium-potassium-ATPase, sodium-potassium co-transport, sodium-calcium exchange, and calcium membrane binding were suggested as possible causes.

Conversely, the high serum ionized calcium observed in high-renin hypertensives was suggested to reflect an increase in dissociation of calcium from intracellular binding sites with subsequent release into the blood. In this form of hypertension, renin may be the driving force, inducing the hypertension and, concomitantly, causing shifts in ion fluxes resulting in higher levels of serum ionized calcium and lower levels of serum magnesium. The high-renin hypertension, in some cases,

could be due to occult hyperparathyroidism which would result in high serum ionized calcium and low serum magnesium. Also, the suggestion is made that PTH may directly stimulate renin secretion (19).

E. Calcium, Pregnancy, and Toxemia of Pregnancy

Toxemia includes both eclampsia and preeclampsia. Eclampsia is one of the most serious obstetrical complications. Its symptoms include convulsions, edema, proteinuria, and hypertension. It is accompanied by approximately 30-35% fetal mortality and about 10% maternal mortality (49). The incidence of eclampsia is generally low in industrialized countries and is higher in poor developing countries where low socio-economic status, poor prenatal care, and poor nutrition are common (49,50).

The existence of a link between calcium intake and toxemia of pregnancy was postulated between 1930 and 1960. Interest in this link subsequently waned, however, due to the inability to produce convincing evidence of its existence (50). This connection is again being reviewed.

Villar et al. (49) studied calcium intake and eclampsia rates in the U.S. and two South American countries, Guatemala and Colombia. In the U.S., 21,215 deliveries were studied. In Guatemala and Colombia, the samples were 49,342 and 138,215 deliveries respectively. In the U.S., 16 cases of eclampsia were found, yielding a rate of 0.075%. In Guatemala, 41 cases were found for a rate of 0.083%, and in Colombia, 220 cases were found for an eclampsia rate of 0.159%. The eclampsia rates for the U.S. and Guatemala were not significantly different. The rate for Colombia, however, was significantly higher than for both the U.S. ($p<0.003$) and Guatemala ($p<0.001$). Dietary intake of calcium was assessed by 24-hour dietary recall in Colombia, and this data was checked against a smaller sample of families whose food preparation and intake were observed

directly. In Guatemala, a seven-day dietary record was used with a nutritionist visiting the families each day to observe preparation and weigh different food items. In the U.S., seven-day dietary recall was used. Table II (50) compares eclampsia rates and dietary calcium intake for these three countries, and seven others as well. As can be seen, the eclampsia rates are higher in countries where the calcium intake is low and lower in countries where calcium intake is high. The eclampsia rate for the U.S. used in the table comes from a different study by the same authors (49). The authors noted certain problems inherent in food recall surveys, including faulty or selective memory, reluctance to reveal what was eaten, report of an atypical day, or desire to "please" the interviewer. They noted, however, that estimates based on recall and perhaps fortified by observational data remain the most reliable method of assessing nutrient intake available.

Table II. Relationship between incidence of eclampsia and daily calcium intake per inhabitant in different countries

Country	Daily calcium intake/ person (mg)	Eclampsia incidence of births (‰)
Colombia	240	1.59
Thailand	266	3.7–6.0
Jamaica	345	2.5
India	347	12.0
Japan	368	High incidence
Israel	884	0.7
United Kingdom	1000	0.9
Ethiopia	1075	0.9
USA	1100	0.5
Guatemala	1100	0.58–0.83

$R_s = -0.86, P < 0.01$ (Spearman-Rank correlation coefficient).

(Data from reference 49)

In Guatemala and Colombia, the intake of calories, protein, vitamin A, thiamine, riboflavin, niacin, and vitamin C were significantly less than in the U.S. (49). Calcium intake, however, was much higher in Guatemala than in Colombia and was comparable to that in the U.S. The reason for the high intake of calcium in Guatemala was the tortillas which constitute at least 50% of daily food intake. These tortillas are made

by soaking and then cooking corn in lime water (calcium hydroxide). A typical tortilla contains about 196 mg of calcium per 100 grams of tortilla as compared to only 4 mg calcium per 100 grams of corn before preparation. Ethiopians, who display a low rate of eclampsia, have as a staple of their diet a grain called teff, which contains about 110 mg calcium per 100 grams of grain (49). Three possible confounding factors--age, parity distribution, and prenatal care--were analyzed for the three countries of Guatemala, Colombia, and the U.S. When corrections for these were made, the significance in eclampsia rate differences remained.

These data, however, are epidemiologic and, as the epidemiologic data discussed previously, cannot prove a cause-effect relationship. They can only point the way to research designed to show such a relationship (49).

Varner et al. (51) performed a study designed to determine whether any alterations in perinatal calcium metabolism occur in pregnancies complicated by maternal essential hypertension. Subjects consisted of 17 pregnant women with essential hypertension, analyzed before and after delivery, and their infants. No definition of hypertension or the blood pressures of the patients were given. None of the women had other evidence of preeclampsia. Controls consisted of normotensive pregnant women and their infants in a previous study by some of the same authors. Blood analysis before delivery revealed significant differences between hypertensive and normotensive mothers. Hypertensive mothers had lower levels of parathyroid hormone (PTH) (28.2±22.3 vs 62.7±11.2 mEq/l for normotensives) ($p<0.01$), serum ionized calcium (2.09±0.11 vs 2.27±0.25 Eq/l for normotensives) ($p=0.02$), and albumin (2.94±0.30 vs 3.32±0.45 gm/dl for normotensives) ($p=0.01$), and higher levels of phosphorus (5.27±0.67 vs

4.09±0.74 mg/dl for normotensives) ($p<0.001$). Within two minutes after delivery, maternal blood was again drawn. In addition to the differences shown above, calcitonin was significantly lower (140.5±64.4 vs 197.9±36.7 pgm/dl for normotensives) ($p<0.01$) in hypertensives. Umbilical arterial and venous blood were analyzed and showed that the fetuses of hypertensive mothers also had depressed levels of PTH and ionized calcium and elevated levels of phosphorus. No significant differences were found between neonates of the two groups at 24 hours of age. Serum magnesium, total calcium, and total protein showed no significant differences in either mothers or fetuses.

The low PTH levels found in hypertensives in this study contrast with the higher PTH levels found in nonpregnant hypertensives by McCarron et al. (30) and Strazzullo et al. (31). The authors (51) suggested that there may be a pregnancy-specific factor involved in this outcome. They suggested that the hypertensive patients may have had limited extracellular volume expansion relative to normotensive controls, and that this might result in a decreased requirement for additional serum ionized calcium. Such decreased requirement for ionized calcium could explain in part the lowered PTH levels in hypertensive patients. Pregnancies complicated by hypertension also may be associated with diminished estrogen production. Because estrogens are known to inhibit the bone resorptive effects of PTH, a decrease in their levels may be expected to decrease the expected compensatory increased levels of PTH (51). This, in turn, could lead to decreased serum ionized calcium.

Resnick et al. (52) attempted to define further some of the abnormalities of calcium metabolism in preeclampsia. Subjects were nine preeclamptic and eight normal pregnant patients. All subjects were in

the third trimester of pregnancy. Fasting measurements were taken of urinary sodium and calcium, serum ionized calcium, serum magnesium, PTH, and plasma renin activity.

Urinary sodium excretion was not different in the two groups. Significant differences were found for all other parameters, however. Urinary calcium (34±12 vs 296±46 mg/day for normotensives) ($p<0.001$), serum ionized calcium (2.13mEq/l for hypertensives and 2.33 mEq/l for normotensives) ($p<0.001$), and plasma renin activity ($p<0.02$) were all lower in preeclamptic subjects, while PTH ($p<0.01$) and serum magnesium ($p<0.05$) were higher in these subjects. The lowered urinary calcium excretion found contrasts with other studies (29-31,42,43) involving nonpregnant subjects in which hypertensives had significantly higher levels of urinary calcium. The lowered serum ionized calcium in preeclamptic subjects was in agreement with Varner et al. (51) while the elevated PTH levels in these subjects disagree with the findings of Varner et al. (51). The elevated PTH levels agree with other studies of nonpregnant subjects (30,31). In agreement with Resnick et al. (19), plasma renin activity was positively correlated with serum ionized calcium and negatively correlated with serum magnesium. The authors (52) suggested that monitoring serum ionized calcium and/or urinary calcium excretion may be of diagnostic value in early preeclampsia, and that calcium loading may be of value in the prevention and/or treatment of this condition.

Richards et al. (48) compared serum levels of calcium in 16 normal pregnant women, 12 pregnant women with chronic hypertension, and 31 women with pregnancy-induced hypertension. Of the latter group, 20 had mild to moderate preeclampsia and 11 had severe preeclampsia/eclampsia. Serum

total calcium, ionized calcium, magnesium, phosphorus, total protein, and albumin were measured.

No significant differences were found for any of the parameters except total protein which was significantly lower (5.5 vs 6.3 gm/dl for normotensives) ($p<0.05$) in the 11 subjects with severe symptoms. Serum ionized calcium was slightly, but not significantly, higher in subjects with chronic hypertension or mild to moderate preeclampsia (2.46 mEq/l for both groups as compared to 2.40 for normotensives). Of interest is a comparison of this study with those of Varner et al. (51) and Resnick et al. (52). While significant differences were found in serum ionized calcium concentrations between hypertensive pregnant patients (51) and preeclamptics (52) when compared with normotensive pregnant patients, values for all groups in both studies (51,52) fell within the normal nonpregnant range for serum ionized calcium as given by Richards et al. (48). Although no significant differences in serum ionized calcium were found between normal pregnant women and those with mild to moderate preeclampsia (48), the average value for the normal subjects was at the very top of the range for nonpregnant normal subjects while that for the preeclamptic subjects was slightly above this range. Possibly differences in analytical techniques could account for those findings. Details of those techniques were not given in all cases, however. Meaningful interpretation of the comparison of these studies (48,51,52), therefore, probably is not possible.

No studies were found involving calcium supplementation in pregnant patients with toxemia. Belizan et al. (32), however, reviewed the effects of calcium supplementation on blood pressure in normal pregnant patients. Thirty-six Guatemalan pregnant women, ages 20 to 35 years, were divided

into three treatment groups. Subjects received either one gram of calcium per day, two grams of calcium per day, or a placebo. Treatment lasted from weeks 15 to 36 of gestation. Calcium intake at baseline, as determined by 24-hour dietary recall, was not significantly different in the three groups. Blood pressures of the three groups at baseline also were not significantly different. Figure 7 (32) shows the changes in systolic blood pressure of the three groups during treatment. The control group's mean systolic blood pressure oscillated around the baseline value while both supplemented groups tended to have reductions in systolic blood pressure during the second trimester. Near the end of the third trimester, systolic blood pressures of the control and one-gram calcium groups were again similar. The two-gram calcium group, however, maintained significantly lower blood pressures than the other groups during the third

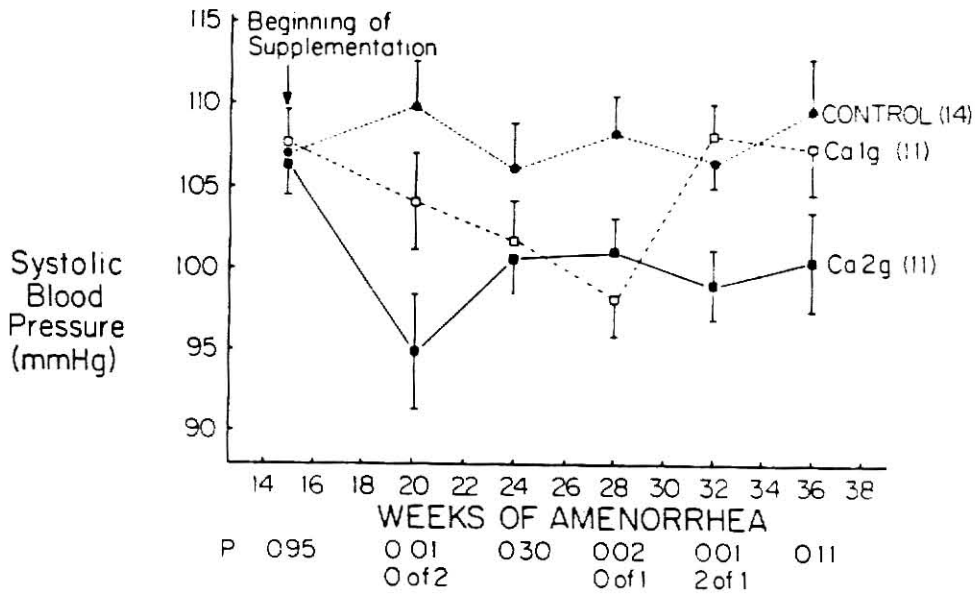

Fig. 7. Means and SEs for systolic blood pressure measured in the lateral position at different points during pregnancy are presented. The control group showed fluctuations in its values throughout pregnancy. The two supplemented groups had a significant reduction by the second trimester (lowest points at 20 weeks for the 2 gm of calcium group and at 28 weeks for the 1 gm of calcium group). By the thirty-second week the 1 gm of calcium group had reached the control group's values. The 2 gm of calcium group continued to have lower mean values throughout the third trimester.

(Data from reference 32)

trimester. Diastolic blood pressures showed similar trends throughout treatment, with the two-gram calcium group maintaining significantly lower values than the other groups during the third trimester.

Serum total calcium and PTH levels also were measured. No significant differences in either of these were found. PTH levels, however, showed interesting trends. The third trimester of pregnancy is a stage of major calcium adjustments, with increased fetal demand, increased estrogen production which inhibits bone resorption, and the need for increased intestinal absorption of calcium. All of these lead to increased PTH levels which peak at term in normal pregnancies. This trend was found in the control group, whereas the two-gram calcium group showed a decrease in PTH levels from week 15 to term, though none of the values reached significance. No change in PTH levels was found in the one-gram calcium group (32).

F. Calcium Supplementation and Blood Pressure

Several animal studies have shown an attenuating effect on blood pressure with calcium supplementation (18,33,53,54). Most such studies have involved the spontaneously hypertensive rat (SHR), which is genetically predisposed to develop hypertension. Placing this animal on a calcium supplemented diet will lower its blood pressure even though the diet is not introduced until 10-12 weeks of age (WOA), when hypertension is established (33,54). Conversely, calcium restriction will accelerate the development of hypertension (18). The earlier in life the calcium supplementation is started, the greater will be the lowering of blood pressure. McCarron (18) divided 12 SHRs into three groups. Each received either a .25% calcium diet (low normal), a .5% calcium diet (normal), or a 4.0% calcium diet (supplemented). Treatment began at seven WOA and

continued to 39 WOA. Between WOA seven and 17 the rise in systolic blood pressure in the three groups was similar. Values at seven WOA were 131, 138, and 125 mmHg for the 4.0%, .5%, and .25% calcium groups, respectively. At 17 WOA, values were 171, 174, and 185 mmHg, respectively. Thereafter, this parameter tracked inversely with the calcium content of the diet ($p<0.001$). At 39 WOA, systolic blood pressures of the three groups were 154, 176, and 181 mmHg for the 4.0%, .5%, and .25% calcium groups, respectively. Diastolic blood pressure was not discussed. In another study, McCarron (53) observed the effect of calcium supplementation on blood pressure in the Wistar-Kyoto rat, the normotensive genetic control for the SHR. Diets of varying calcium content, as above (18), were fed to the animals starting at 8-10 WOA and continuing to 34 WOA. By 12 WOA, significant differences in systolic blood pressure ($p<0.01$) were observed between the three groups (115, 120, and 124 mmHg for the 4.0%, .5%, and .25% calcium groups, respectively). Again, diastolic blood pressure was not discussed. At 34 WOA the 4.0% calcium group had the lowest systolic blood pressure (110 mmHg), while those of the other groups were 114 and 124 mmHg for the .5% and .25% calcium groups, respectively.

Two studies have assessed the effects of calcium supplementation in human hypertensives (29,55). One (29), however, discussed only its effects on urinary calcium excretion and not those on blood pressure. McCarron et al. (55) assessed the effects of calcium supplementation (one gram per day for eight weeks) on blood pressure in 39 hypertensives and 31 normotensive controls in a double-blind randomized placebo-controlled trial. Compared to baseline ($p<0.05$) and placebo ($p<0.04$), calcium lowered systolic blood pressure in hypertensives, but not in normotensives. Diastolic blood pressure was not significantly changed in either

group. Mean systolic and diastolic blood pressures were not given for the hypertensives and normotensives. A "response to treatment" was defined as a reduction in mean blood pressure of $\geq$10 mmHg. Using this definition, 42% of hypertensives responded while 13% of normotensives did so. In hypertensive respondents, blood pressure went from 145/84 to 128/90 mmHg. In normotensive respondents, blood pressure went from 105/65 to 87/70 mmHg.

McCarron et al. (56) looked at the blood pressure response to calcium supplementation plus one of three drugs in 81 older women (mean age 65 years) undergoing treatment for osteoporosis. All subjects received calcium supplements of one to two grams daily along with either calcitonin, stanozolol (an anabolic steroid) or a placebo. Treatment lasted two years. Those receiving calcium plus placebo had no change in mean arterial pressure (102±10 mmHg at baseline for all subjects). Those on calcium plus stanozolol and calcium plus calcitonin acquired significantly different mean arterial pressures (112±11 mmHg for the stanozolol group and 93±31 mmHg for the calcitonin group) ($p<0.01$). A compensatory increase in PTH levels was found in the calcitonin group, but not in the other groups. The authors suggested that this increase in parathyroid hormone may account for the reduced mean arterial pressure in the calcitonin group. This is in contrast to other studies (30,57), whose authors suggested that PTH may lead to increased vascular tone.

Belizan et al. (57) studied the effects of calcium supplementation on blood pressure in young normotensive men (n=28) and women (n=28). Subjects were divided into two groups, one receiving one gram of calcium per day, the other, a placebo. Treatment lasted 22 weeks. During baseline (eight weeks prior to beginning of treatment), no significant differences were

found for any variable measured except systolic blood pressure in the dorsal position in men ($p<0.05$). Blood pressures at baseline, in mmHg were, for men: 117.8/74.1 (calcium) and 109.0/68.1 (placebo), and for women: 104.1/69.0 (calcium) and 100.2/67.5 (placebo).

In the supplemented women, significant declines were found in both systolic ($p<0.01$) and diastolic ($p<0.01$) blood pressures. The decline in diastolic blood pressure was 5.6%, with that of systolic being somewhat less. Women on the placebo had no significant changes in blood pressure. In men, diastolic ($p<0.01$), but not systolic blood pressure, was significantly lower (by 9%) in the supplemented group, while no significant changes in blood pressure occurred in the placebo group. These findings contrast with those involving the osteoporotic patients (56) in which no significant changes occurred in the group receiving calcium and placebo. The osteoporosis or the large difference in ages of the subjects in these studies (56,57) may account for the differences in response. These findings (57) also contrast with those of McCarron et al. (55), in which normotensives as a whole did not have significant blood pressure reductions. Neither the ages nor sex distribution of these subjects (55) were given, however, so that possible explanations for the different outcomes are not readily available.

G. Abnormalities of Calcium Metabolism in Hypertension

A number of abnormalities of calcium metabolism have been found in experimental and/or human hypertension and have been postulated to play a role in its pathogenesis. These include multiple defects in membrane and cytosolic metabolism of calcium (18,58), increased urinary losses of calcium (29-31), increased parathyroid hormone (PTH) levels (30,31,52),

increased serum total and ionized calcium (19,46), and decreased serum ionized calcium (44,51,52).

Defects in membrane and cytosolic metabolism of calcium in the spontaneously hypertensive rat (SHR) included increased calcium permeability of the plasma membrane, reduced calcium binding to isolated membranes following incubation, altered intracellular fluxes of calcium between cytosol and various intracellular compartments, and increased total calcium content of the cell (18). In vitro preparations of plasma membrane from hypertensive animals, bathed with the isotope ^{45}calcium revealed a decrease in binding sites for this isotope (18). A decrease in binding of calcium to the plasma membrane, along with increased permeability of the membrane to calcium, would logically lead to an increase in intracellular ionized calcium. This in turn would lead to increased interaction of calcium with calmodulin and result in increased actin-myosin interaction and increased vascular tension. McCarron (18) suggested that calcium in the plasma membrane may be the ultimate regulator of fluxes of both calcium and other ions across the membrane. Sufficient membrane-available calcium will inhibit calcium fluxes, while conditions causing decreases in membrane-available calcium may stimulate calcium fluxes, resulting in increased permeability to calcium and other ions with a consequent increase in vascular tension (18). In addition, Kwan et al. (58) found a decreased ATP-dependent transport of calcium by arterial plasma membranes in the SHR. This would seem to imply a defect in the ion pump responsible for extruding calcium from the cell.

In humans, less is known about cellular aberrations of calcium metabolism in hypertension. Erne et al. (59,60) have studied cellular calcium handling in blood platelets of human hypertensives and

normotensives. Platelets were chosen because they are easily obtainable and have a number of similarities to vascular smooth muscle, including a calcium-dependent contractile process. Significantly increased ionic calcium concentrations were found in the platelets of the hypertensives (168±32, 127±10, and 108±16 nmol/cell for those with established hypertension, borderline hypertension, and normotensives, respectively) ($p<0.001$). These concentrations correlated closely with blood pressure. Treatment with antihypertensive drugs decreased both blood pressure and intracellular free calcium. Suggested mechanisms which could explain the increased free calcium content of the platelets of hypertensives included increased membrane permeability of calcium or defects in ionic membrane pumps leading to increased intracellular sodium, and consequently, increased intracellular calcium (59,60). Natriuretic hormone also may be a factor by inhibiting sodium-potassium-ATP-ase activity, which is responsible for maintaining cellular sodium balance (61). Inhibition of this enzyme would lead to increased intracellular sodium, inhibiting calcium extrusion, thus causing an accumulation of calcium as well. Increased free calcium would in turn lead to increased vasoconstriction.

Three studies (29-31) have documented an increased urinary loss of calcium in human hypertensives. Morris et al. (29) found a 63% increase in urinary calcium in hypertensives as compared to normotensives, in spite of a lower calcium intake by the hypertensives. In another study (30) McCarron et al. suggested that the cause for this increased urinary calcium in hypertensives is a defect in the distal tubule of the nephron resulting in an inability to reabsorb calcium adequately. Strazzullo et al. (31) suggested a similar defect, but in the proximal rather than the distal tubule of the nephron. McCarron et al. (30) and Strazzullo et al. (31)

both found direct correlations of urinary calcium with urinary sodium in hypertensives and normotensives. The ratio of urinary calcium to urinary sodium, however, was increased in the hypertensives. This would seem to indicate an important role for proper sodium metabolism in the maintenance of normal calcium balance.

Increased PTH levels have been found in nonpregnant (30,31) and pregnant (52) hypertensive humans. This hormone's main function is to keep serum ionized calcium at the proper level by simulating bone resorption when serum ionized calcium is low. It also enhances renal reabsorption of calcium. Both of these attributes were suggested by McCarron et al. (30) as the mechanisms compensating for the increased urinary calcium losses in the hypertensives. This would account for the increased PTH levels found in the hypertensives. Strazzullo et al. (31) also suggested PTH's stimulation of renal calcium reabsorption in the face of increased urinary calcium losses as the reason for its elevated levels in the hypertensives.

Parathyroid hormone has variously been suggested to have both vasopressive (19,30,31,32,57,59) and vasodilator (18,22,30,62) properties. Belizan et al. (32) and Strazzullo et al. (31) noted studies that have shown a vasopressive action for PTH in rats. Parathyroidectomized genetically hypertensive rats developed hypertension to a milder degree than did rats with intact parathyroid glands. On the other hand, McCarron (18,22) noted studies showing a vasodilatory effect for PTH in both rats and humans. The authors of three studies (31,57,59), who suggested a vasopressive role for PTH said this hormone may stimulate increased intracellular calcium in vascular smooth muscle, as has been shown in other cell types (57). In kidney and liver cells PTH enhances the permeability

of the cell membrane to calcium. It also stimulates the production of cyclic adenosine monophosphate (cAMP). This compound then stimulates the efflux of calcium from mitochondrial stores, further increasing intracellular free calcium (57). If this occurs in vascular smooth muscle, a vasopressive action would be understandable. However, van Breeman et al. (63) imputed to cAMP a probable vasorelaxing role via stimulation of calcium uptake by the sarcoplasmic reticulum, and possibly by direct inhibitory action on smooth muscle contractile proteins. No mention was made of PTH (63). Resnick et al. (19) noted that angiotensin II (AII) releases bound intracellular calcium stores, contributing to increased vascular tension. AII production is stimulated by renin, which in turn has been suggested to be increased directly as a result of PTH stimulation.

In SHRs, Grady and McCarron (62) found a vasodilatory effect of PTH. This effect was greater in animals on a high calcium diet (4.0% of diet) than in those on a calcium depleted diet (.01% of diet). The authors, as well as McCarron (22), suggested that the vasodilatory effect of PTH is greatest in states of adequate calcium intake, and that calcium depletion seriously diminishes this effect. No mechanism for this effect of PTH was proposed. An explanation to reconcile these divergent reports of the effects of PTH on blood pressure is not readily apparent.

McCarron (44) found lower serum ionized calcium in human hypertensives as compared to normotensives. He also noted studies with the SHR showing this as well. He suggested that this may reflect enhanced bonding of calcium to extracellular protein, leaving total serum calcium unchanged. The mean value for serum ionized calcium in the hypertensives, however, was within the normal range as given by Richards et al. (48). Varner et al. (51) and Resnick et al. (52) found lower serum ionized

calcium in pregnant hypertensives compared with normal pregnant patients. In both cases, however, the values for the hypertensives were within the normal range. Fogh-Andersen et al. (47), however, found no significant difference in serum ionized calcium between nonpregnant hypertensives and normotensives, and suggested that in McCarron's study (44), the blood samples may not have been handled and stored in the same way, which may have caused the differences found. Hawthorne et al. (46) found increased total serum calcium among hypertensives but offered no explanation to account for this. A number of other studies (30,31,32,48) have shown no differences in serum calcium levels of hypertensives and normotensives. In three of these (30-32), PTH levels were elevated in the hypertensives, which might have compensated for serum calcium values which otherwise would have been low. Resnick et al. (19) found lower serum ionized calcium in low-renin hypertensives and high serum ionized calcium high-renin hypertensives. The low serum ionized calcium in the low-renin hypertensives was thought to reflect increased levels of intracellular free calcium, which would result in increased vasoconstriction. The high renin levels in the high-renin hypertensives might be the result of increased PTH levels (though PTH was not measured). Whatever the cause, increased renin levels, along with low serum levels of magnesium (as was found), would lead to increased AII levels. This would stimulate the release of bound intracellular calcium stores, some of which apparently would be released from the cells, giving rise to the higher serum levels of this cation. Many components and interrelated mechanisms may be involved in the genesis of the hypertension, and much work remains to be done in decifering the causes of all the metabolic abnormalities of

calcium and other components involved in blood pressure regulation, which give rise to hypertension.

V. Summary and Conclusions

Hypertension is a condition affecting approximately 25 million Americans. It is almost without symptoms, yet greatly increases the risks of stroke, heart attack, and heart and kidney failure; hence the name "the silent killer." The incidence of hypertension has gone down in recent years. Nevertheless it continues to be a major health problem in the U.S.

In the past, sodium has received much attention in relation to high blood pressure. A reduction in sodium intake has often been advised for patients with hypertension. In recent years the role of calcium in blood pressure regulation, and its relation to hypertension, have received increasing attention. Calcium is very important to normal cardiovascular physiology, and is essential, via both membrane and cytosolic-related mechanisms, in the function of vascular smooth muscle cells. Interest in the role of calcium in blood pressure regulation and hypertension was initiated after a number of epidemiologic studies showed a negative correlation between cardiovascular disease mortality rates and water hardness, of which calcium and magnesium are the main determinants (23-26,34-37). Dietary surveys of calcium intake and blood pressure (3, 41), as well as studies comparing the calcium intake of hypertensives versus that of normotensives (16,41), have shown significantly lower intakes among hypertensive subjects, suggesting a protective effect for calcium. In addition, supplementation of the diet with calcium has been shown to decrease blood pressure in hypertensive (18) and normotensive

(53) rats and in hypertensive (55) and normotensive (32,57) humans. Studies of both hypertensive animals and humans have linked several abnormalities of calcium metabolism to this condition. Urinary calcium excretion was found significantly higher in hypertensives (30,31), along with elevated levels of PTH, probably as a response to the increased urinary calcium losses. PTH has been suggested to have both vasopressive (19,30-32,57,59) and vasodilatory (18,22,30,62) properties, but no explanation to reconcile these divergent reports is as yet available.

The aspect of calcium metabolism in hypertension about which the greatest uncertainty remains seems to be the serum levels of this cation. Serum total calcium has been reported as increased (42,45,46) and unchanged (30,31,44). Serum ionized calcium has been reported as increased (47), decreased (44), or unchanged (31) in nonpregnant hypertensives, and decreased (51,52) or unchanged (48) in pregnant hypertensives.

Defects at the cellular level have been found in genetically hypertensive rats, including increased calcium permeability of the plasma membrane, reduced calcium binding to isolated membranes following incubation, altered fluxes of calcium between cytosol and various intracellular compartments, increased total calcium content of the cell (18), and decreased ATP-dependent transport of calcium by the plasma membrane (58). Studies in hypertensive humans using blood platelets, which are similar in several ways to vascular smooth muscle, have suggested that these defects may occur in humans as well.

Much remains to be learned about the physiology and biochemistry of calcium's relation to blood pressure regulation and hypertension. The bulk of evidence compiled so far, however, strongly suggests that obtaining adequate calcium in the diet may be an important factor in maintaining

normal blood pressure. Also, supplementation with this nutrient, in view of the fact that no side effects were reported in the literature reviewed, may be a valuable nonpharmacological tool in the treatment of hypertension.

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CALCIUM AND HYPERTENSION

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Hypertension is a major health problem in the U.S., affecting approximately 25 million Americans. It greatly increases the risks of stroke, heart attack, and kidney and heart failure. Excess sodium has long been thought to be one of the major etiologic factors in this condition. In recent years, calcium and its role in blood pressure regulation and hypertension have been the subject of increasing study. Interest in this area was initiated after a number of epidemiologic studies showed negative correlations of cardiovascular disease mortality rates with water hardness. Dietary surveys of calcium intake and blood pressure, as well as studies directly comparing the calcium intake of hypertensives with that of normotensives have shown lower intakes of this nutrient among hypertensives. Supplementation of the diet with calcium in both hypertensive and normotensive animals and humans has lowered blood pressure. Several abnormalities of calcium metabolism have been reported in hypertension. These include increased urinary losses of calcium, increased PTH levels, alterations of serum levels of total and ionized calcium, and membrane and cytosolic defects of vascular smooth muscle cells. Defects found in vascular smooth muscle cells of hypertensive rats include increased permeability of the cell membrane to calcium, reduced binding of calcium to isolated membranes following incubation, altered fluxes of calcium between cytosol and various intracellular compartments, increased total calcium content of the cell, and decreased ATP-dependent transport of calcium by the plasma membrane. Studies in human platelets, which are similar to vascular smooth muscle cells, indicated that similar abnormalities may occur in human vascular smooth muscle. Much remains to be learned about calcium metabolism in blood pressure regulation and hypertension. Most of the evidence compiled thus far, however, strongly suggests that an

adequate intake of this nutrient may be important in the maintenance of normal blood pressure. In addition, supplementation with calcium may be a valuable therapeutic tool in the treatment of hypertension.