Renal - Hypertension

NEW INSIGHTS INTO THE PATHOGENESIS OF HYPERTENSION: THE ROLE OF SODIUM AND CALCIUM

MEDICINE GRAND ROUNDS
November 18, 1982
Norman M. Kaplan, M.D.

I. Probable Causal Mechanisms of Primary Hypertension

   A. Increased sodium, decreased potassium intake
   B. Stress
   C. Genetic predisposition

II. The Presence of Increased Intracellular Sodium

III. The Presumed Role of Natriuretic Hormones

IV. An Integrated Scheme for the Pathogenesis of Primary Hypertension

V. The Sites of Action of Antihypertensive Agents

VI. The Potential for Prevention

"If too much salt is used in food the pulse hardens....When the heart pulse beats vigorously and the strokes are markedly prolonged, the corresponding illness makes the tongue curl up and the patient unable to speak."
The Yellow Emperor's Classic in Internal Medicine, 2600 B.C.

"Evidence that sodium consumption is a major factor in causing hypertension is not fully conclusive. The evidence is strong enough, however, for most members of the medical and scientific community to conclude that a substantial protion of th U.S. population which is predisposed to hypertension would benefit from reduction in sodium."
Preamble to FDA's proposed 1982 sodium regulation.

"General, moderate reduction in dietary salt intake cannot predictably be anticipated to decrease the development of hypertension. The role of the diet in the cause or prevention of hypertension has not yet been defined.
W.J. Darby in Contemp. Nutr. 5:1, 1980

"Among patients with systolic hypertension, one finds an unusual frequency of those who as directors of big enterprises had a great deal of responsibility and who after a long period of psychic overwork, became nervous."
W. Geisback in Dtsch. Arch. Klin. Med. 83:363-374, 1905

"I confess I am inclined to believe that the kidney is the chief promotor of the other derangements."
R. Bright in Guys Hosp. Rep. 1:380, 1836

Over the past few years, a large amount of new experimental evidence has engendered enthusiasm over the prospect that the pathogenesis of primary (essential) hypertension may finally be understood. These observations have not been coordinated into a proved pathogenetic scheme, but at least some of them have been combined into logical hypotheses (Haddy and Overbeck, 1976; Blaustein, 1977; de Wardener and MacGregor, 1980). Though some of the pieces and connections remain unproved, there are enough solid data to warrant a review of the current evidence and the presentation of a more inclusive pathogenetic scheme. What follows may be a premature and overly enthusiastic acceptance of preliminary data in the hope that the mystery of primary hypertension may soon be revealed. Even if it all doesn't hold together, the hypothesis has such broad explanatory power that it will almost certainly gain primacy in the hierarchy of hypotheses.

As it is presented, it will be obvious that some of the previously held concepts are excluded. These include autoregulation (starting with an elevated cardiac output), mineralocorticoid excess and disturbed renin profiles. With no firm evidence for their role, there seems no need to carve a place for them, particularly since the hypothesis holds together well without them.

I. Probable Causal Mechanisms of Primary Hypertension

On the basis of more and more long-term observations, primary hypertension can be characterized as a slowly progressive, markedly variable rise in both systolic and diastolic blood pressure, often beginning in early childhood though usually not obvious until mid-life. If hypertension is defined as the level of blood pressure beyond which the benefits from treatment outweigh the risks of non-treatment, a sustained average level of 140/90 for those below age 40 and 150/95 for those beyond seem to be reasonable criteria. If primary (essential) hypertension is defined by the absence of recognizable features of specific secondary mechanisms, almost 95 per cent of those with an elevated blood pressure have "primary" hypertension.

The need to recognize its causes and thereby apply preventive measures is obvious: it has a high frequency, about 15% of the adult population; it poses significant risks for premature cardiovascular disease, and there are potential hazards of currently available antihypertensive drug therapy, as discussed in my Grand Rounds of April 30, 1981 and elsewhere (Kaplan, 1982). In this Rounds, the three causal mechanisms for which there is greatest support will be covered.

A. Increased Sodium, Decreased Potassium Intake

The first known presentation of the idea that dietary sodium causes hypertension is found in The Yellow Emperor's Classic in Internal Medicine, written in 2600 B.C. (Veith, 1966) (see page 1).

The idea keeps coming back, and over the past 10 years, it has received increasing support. A decrease of potassium intake almost always accompanies an increase in sodium intake and some believe the decrease in potassium is as important as the increase in sodium (Meneely

and Battarbee, 1976; Lever et al, 1981). Lewis Dahl was the most persistent advocate, and his life-long work is only now receiving widespread acceptance (Dahl, 1972; Bulpitt, 1981).

1. Historical evidence of change in diet

Our nomadic ancestors, who ate meat when their hunt was successful, likely had an average daily intake of about 60 mmol of sodium and 200 mmol of potassium. When agriculture developed, the intake of sodium by herbivorous people likely fell to an average of 10 mmol/day. Bunge in 1902 postulated that the appetite for sodium arose from the need of herbivorous people to more effectively excrete their large loads of potassium.

However, the best anthropological data suggest that cultural habits, not physiologic needs, were the main determinants of man's appetite for sodium (Fregley, 1980). Groups who remain primitive continue to subsist on a very low sodium-high potassium diet. Some, such as the Yanomamo Indians in South America, often run 50 miles a day in a tropical climate while ingesting an extremely low sodium diet, reflected in 24 hour urines containing an average of 1.5 mmol of sodium (Oliver et al, 1975).

With domestication, the need to preserve food that was hunted or gathered "in season" became desirable and the use of sodium chloride increased. Thereby, the taste for sodium was acquired. Those who do not use it dislike it when it is first introduced but, in a relatively short time, habituation develops in a manner analagous to the use of tobacco, coffee and alcohol (Hollenberg, 1980). About 2400 years ago, Job asked "Can that which is unsavory be eaten without salt?"

We have no certain knowledge of any changes in sodium intake in more recent times or of changes in the incidence of hypertension. But we are clearly ingesting 5 to 20 times more sodium than our ancestors did and we have more than enough hypertension. With the increased use of processed foods over the past 50 years, our diets have very likely become higher in sodium and lower in potassium (Table 1)

Table 1: Comparison of Sodium and Potassium in Processed and Unprocessed Foods (mg/100g)

Unprocessed foods	Na	K	Processed Foods	Na	K
Flour, wheat	2	95	White bread	503	100
Rice, raw brown	8	210	Rice, instant	270	trace
Peas, uncooked	2	316	Peas, canned	236	96
Ham, fresh lean	71	288	Ham, cured lean	1,110	340
Beef, lean flank	65	360	Beef, corned	1,310	60

Some have argued that we need these large amounts of sodium to prevent rapid sodium depletion and vascular collapse. However, excess dietary sodium cannot be stored and there is no evidence that those who are on a lesser intake are any more susceptible to depletion during times of increased external losses.

Even during heavy exercise in hot, humid climates, acclimitization minimizes the need for sodium to a few millimoles per day (Conn, 1949). Hollenberg has argued persuasively for a "set-point for sodium homeostasis that lies normally at that total body sodium content where an individual not ingesting sodium has no sodium excretion in the absence of renal or extrarenal losses" (Hollenberg, 1980).

The case has been well stated by Derek Denton:

"High salt intake is essentially a new nutritional situation of the past hundred years or so of civilization. This can be set against the fact that the physiological character of the appetite and regulatory metabolic systems of primates and man have evolved over millions of years under conditions where dietetic Na+ intake has been low and K+ intake high....perhaps the high salt intake from infancy to middle age of a large segment of the population in Western communities is an important factor in the causal expression of....the hypertensive state (Denton, 1976).

One additional point: "Evolution cannot operate to preserve Darwinian fitness if a new environmental factor does not produce manifest disability or death until late middle age" (Trowell, 1980). Therefore, if the excess sodium we now ingest is harmful, it's unlikely to lead to evolutionary changes in "regulatory metabolic systems" or to genetic outbreeding since it doesn't affect reproductive capacity or survival into middle age.

2. The blood pressure of low sodium, high potassium populations

Table 2 is a partial listing of the populations scattered over the earth who have been eating low sodium, high potassium diets. Without exception, they have very little if any hypertension or rise in blood pressure with aging. Most are primitive and are different in many other ways from acculturated societies. Pickering attributed their low blood pressures to the "certainty of behavior in a society ruled by ritual and taboo", versus "the uncertainty in western societies in which life is a series of individual choices and decisions" (Pickering, 1980). One can only wonder if life in primitive times was less stressful than ours.

Table 2: Sodium Intake of Population Characterized by Low Blood Pressure

Society	Sodium (mEq/24 hr)
Yanomamo Indians, Brazil	∿ 1.5
Tukisenta, New Guinea	∿15
Kwaio, Baegu, Aita, Solomon Islands	10-20
Pukapuka, Cook Islands	∿65
Samburu, Uganda	∿50
Ontong Java, Solomon Islands	50
Tarahumura, Mexico	∿85

However, primitive people, such as the Qash'gai nomads of Iran, who eat lots of salt have as much hypertension as acculturated people (Page, 1979). Among equally primitive people, blood pressure varies with sodium intake: two Solomon island groups are very comparable in lifestyle but the Lau cook their food in sea water and have an average sodium intake of 150 to 230 mmol/day and a 9% frequency of hypertension; the Aita use fresh water, have an average sodium intake of 10 to 30 mmol/day and no hypertension (Page et al, 1974).

3. The correlation between sodium and blood pressure (Figure 1)

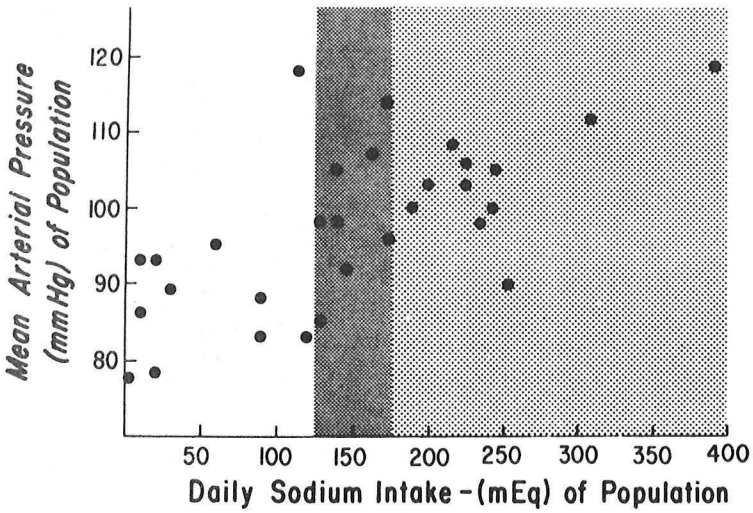

Figure 1: Mean arterial pressure (MAP) vs dietary sodium intake in 30 populations as reported in the literature. MAP is the average of men and women; whenever reported, the 50-59 year old age group is portrayed (From: McCarron et al, 1982).

Depending on how you look at the data, the correlation can be considered strong or weak. More to the point, those populations who consume a fairly high sodium diet have more hypertension than those who consume less than 50 to 75 mmol per day. The sodium intake in almost

all acculturated societies is sufficiently high to be a necessary, though not, in itself, sufficient cause of hypertension. Additional factors, presumably some genetic, must be present to cause a significant minority of those who eat sufficient sodium to become hypertensive. Therefore, no tight correlation should be expected if everyone is beyond the threshold level.

No such data relating potassium intake to blood pressure are available, but in general, potassium intake will vary inversely with sodium intake.

4. Effects of sodium excess in man

Most studies of the effect of large amounts of sodium upon the blood pressure in man are of such short duration as to be of very doubtful pathophysiological significance though some show clear rises in BP in borderline hypertension (Sullivan et al, 1980). However, studies done in Fred Bartter's lab suggest a variable degree of sodium sensitivity (Figure 2) (Fujita et al,1980). Those whose pressures rose on the higher sodium intake had greater sodium retention and a higher degree of sympathetic nervous system drive.

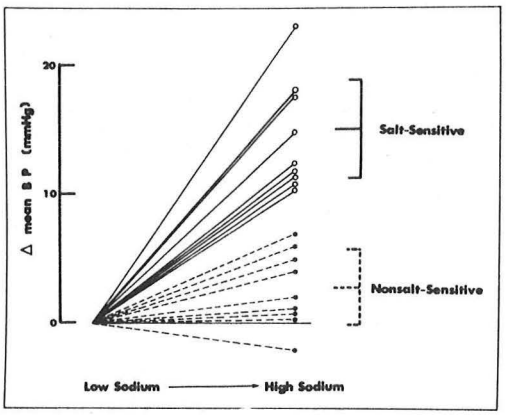

Fig. 2: The change in mean blood pressure in a group of hypertensives from their level while on a 9 mmol per day (low sodium) diet to that while on a 249 mmol per day (high sodium) diet (From: Fujita et al, 1980).

5. Effects of decreasing sodium or increasing potassium intake

A lower sodium intake has been used to treat hypertension since at least 1904 (Chapman and Gibbons, 1949). Most trials prior to 1960 used very low sodium diets, the Kempner rice-fruit protocol having the greatest notoriety. Despite its unpleasantness, it worked (Kempner, 1948). However, the need for a markedly reduced sodium intake (below 30 mmol per day) to achieve an antihypertensive effect was widely quoted. When diuretics became available in the late 50's, the use of such rigidly restricted diets was quickly discarded.

Only recently have proper studies of a more moderately restricted sodium intake been performed (Table 3). Perhaps the best is the randomized, double-blind cross-over trial by MacGregor et al, 1982) (Figure 3).

TABLE 3: Modest Sodium Restriction in Hypertension

Reference	No.	Sodium Excretion (mmol/day) Pre	Post	Duration	Blood Pressure (mm/Hg) Pre	Post
Parijs 1973	17	191	93	4 wks	147/98	-9/6
Carney 1975	19	205	>120 (3) <120 (12)	8 wks	163/106	-15/7
Magnani 1976	37			15-21 mo	166/105	-14/14
Morgan 1978	28	191	157	24 mo	160/97	DBP<95 in 55%
					DBP	DPB
Morgan and Myers 1981	12M <105	197	78	8 wks	97	87
	12F <105	146	58		95	89
	12M >105	171	85		115	103
	12M >105	125	64		111	101
MacGregor 1982	19	191	86	4 wks	156/98	-12/6

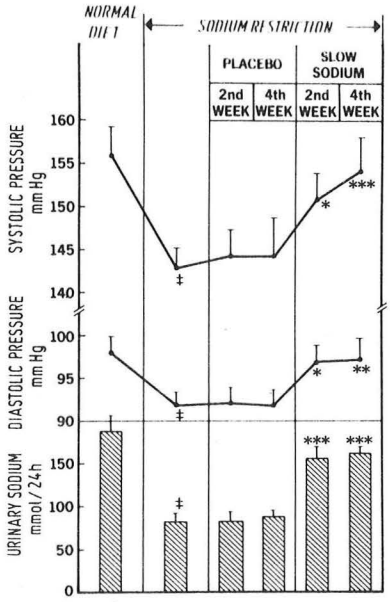

Fig. 3: Average systolic and diastolic blood blood pressure and urinary sodium excretion on normal diet, two weeks on dietary sodium restriction alone, and at two-weekly intervals during the randomized crossover trial of sodium capsules (slow sodium) versus placebo (From: MacGregor et al, 1982).

The modest but significant lowering of the blood pressure observed (from 156/98 to 144/92) is what should be obtainable from the practical, easily attainable reduction of sodium intake to 2000 mg sodium (88 mmol) per day. That degree of BP reduction would, if applied to all of those at risk from hypertension, save more lives than the effective therapy of all patients with significant hypertension (Rose, 1981).

Another randomized trial demonstrated the ability to achieve better control of the BP while reducing the need for antihypertensive therapy (Beard, et al, 1982) (Table 4).

TABLE 4: RANDOMIZED CONTROLLED 12 WEEK TRIAL OF LOW SODIUM DIET

	Urine Sodium		Blood Pressure		Antihypertensives			
					Diuretics		Others	
Week:	0	12	0	12	(Tablets/day) 0	12	0	12
Control	175	161	139/86	133/83	32	27	111	112
Diet	150	37	142/88	131/82	32	1	127	74

"The diet group reported feeling happier and less depressed. Two-thirds intend to condinue diet indefinitiely."

(from: Beard et al.: Lancet 2:455, August 28, 1982)

Much less data are available on the effect of additional potassium intake (Table 5) and the effect may be mediated through a sodium diuresis. The combination of a lower sodium and higher potassium intake resulted in no greater effect than a lower sodium diet alone (Holly et al, 1981).

Table 5: Increased Potassium Intake and Blood Pressure
(20 hypertensives on 280 mmol sodium; 10 day periods)

	K = 75	K = 175
Mean BP	114	103
Body Weight (kg)	61.4	59.9
Mean U_{Na} (10 days)	158	183
Total Exchangeable Na^+	13.6	11.7

(from Iimura et al: Clin Sci 61:77s, 1981)

Evidence incriminating a possible role for lower intake of potassium comes from the correlative studies done by the MRC Blood Pressure Unit in Glasgow: significant inverse correlations between plasma potassium, exchangeable and total body potassium levels with blood pressure were found in hypertensives below age 35, whereas significant positive correlations with exchangeable sodium were found for those over age 50 (Beretta-Piccoli, et al, 1982).

6. Animal Studies

Multiple strains of rats have been found to be sensitive to sodium, the Dahl strain being the most widely studied. These animals, after only three generations of in-breeding, are either resistant (R) or sensitive (S) to a high sodium intake, developing more hypertension the earlier in life the exposure begins. As we shall see, their genetic fault resides in their kidneys.

At least partial protection from sodium induced hypertension can be obtained by feeding extra potassium (Dahl, et al, 1972). This may reflect an increased excretion of sodium. A similar effect of increased dietary calcium has been shown in spontaneously hypertensive rats (Ayachi, 1979).

The last and perhaps most impressive piece of evidence is the presence of increased concentrations of sodium within cells of animals and people with primary hypertension. That evidence will be examined later.

Summary:

The relationship between sodium and blood pressure cannot be conclusively proved to be causal but there is no convincing evidence to disprove the connection. Though the evidence is circumstantial, it is enough to convince most who work in the field. Pickering was a notable exception having great fun at banquets of meetings on hypertension in literally pouring salt on his food. But it's likely that most of us could do the same with no more harm (Sir George died in 1980 at the age of 76, presumably normotensive). Without a certain way to predict who is "sodium-sensitive" however, the wisest course may be to recognize the potential hazard and advise moderation for all, hopefully protecting the 20% who are susceptible, while not harming the rest of us. If one's blood pressure is normal after age 45, it's unlikely that primary hypertension will subsequently develop, so that even moderate sodium restriction would no longer be needed--but by then the desire for sodium may have been so blunted that it would no longer matter.

The evidence concerning potassium is less convincing, mainly because less study has been made of its role. Much of what is claimed to be the effect of increased sodium may, however, be more properly laid to the effect of decreased potassium.

B. Stress

The evidence incriminating stress as an instigator of hypertension is smaller in amount and weaker in content than that for high sodium-low potassium. However, it too has grown considerably in the last few years. The higher prevalence of hypertension in blacks has been attributed to an increased level of suppressed anger and social stresses (Gentry, et al, 1982). Whites who are poor or less educated also have more hypertension (Dyer, et al, 1976).

1. Blood pressure in low stress societies

At least 22 populations who live in small, cohesive, protected circumstances have been found to have low blood pressures which do not rise with aging (Cassel, 1974). Those who abandon such an environment and migrate to more urbanized, disorganized social structures have higher blood pressures which rise with aging (Sever et al, 1980). Obviously, other environmental factors, e.g. sodium intake and obesity, may be involved, but in some the association between hypertension and the stresses of social disorganization seems strong.

2. Hyperresponsiveness to stress in pre-hypertensive man

a. Blood Pressure

Years ago, quantitative responses to stress, e.g. the cold-pressor test, were used in an attempt to predict the development of hypertension but they were not discriminatory. Only recently have more subtle stresses been applied and the results are at least suggestive. As an

example, the stress of mental arithmetic caused a significantly greater rise in the blood pressure of 33 normotensive adolescents with a positive family history (+FH) of hypertension than seen in 25 normotensive adolescents with a negative family history (Falkner et al, 1979).

An even greater rise in blood pressure after mental arithmetic was observed after the +FH adolescents ingested 10 grams of extra sodium chloride for two weeks (Falkner et al, 1981). This apparent interaction between sodium and stress may reflect a heightened sympathetic nervous activation: whereas normals given sodium loads suppress their plasma norepinephrine levels, salt-sensitive hypertensives do not (Campese et al, 1982); increasing sodium intake potentiates the pressor response to exogenous norepinephrine, perhaps reflecting an increase in the number of vascular receptors induced by a high sodium diet (Nadeau et al, 1980).

b. Renal flood flow

During mental stress, normotensives with a positive family history of hypertension had a greater decrease in renal blood flow (RBF) than did normotensives with a negative family history (Hollenberg et al, 1981)(Figure 4).

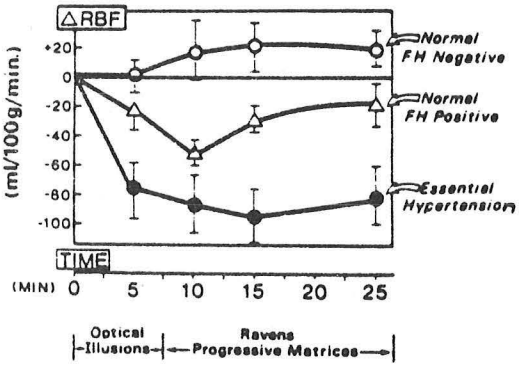

Figure 4 The response of renal blood flow (RBF) to the mild emotional stress provoked by performing a nonverbal IQ test, Raven's Progressive Matrices. (From Hollenberg NK, Williams GH and Adams DF: *Hypertension 3:*11, 1981.)

This study enlarges upon Hollenberg et al's earlier findings of a reduced RBF in early hypertension (Hollenberg et al, 1978). Using radioxenon measurements of RBF, they found an average 20 per cent lower RBF in about two-thirds of 65 hypertensives, all under 35 years of age and most known to have hypertension for less than 2 years, as compared to the levels in 119 normotensives of similar age. The reduced RBF was mediated through the sympathetic nerves since it was rapidly reversible with phentolamine. Such a decrease in RBF, in the presence of a normal GFR, has been assumed to reflect relatively greater constriction of renal efferent arterioles than afferent arterioles and thereby has been held responsible for resetting of the pressure-natriuresis relationship in hypertension.

3. Plasma catecholamines

Of 32 studies, 13 have shown significantly higher plasma norepinephrine levels in hypertensives than in age-matched normotensives (Goldstein, 1981). Young hypertensives have been found to have a super-normal rise in plasma NE after stress (Robertson et al, 1979) and normotensive siblings of hypertensives also may have higher resting plasma NE levels (McCrory et al, 1982). Since so little of the norepinephrine that is released at postganglionic adrenergic nerve endings enters the plasma, plasma epinephrine levels may be a better reflection of overall sympathetic nervous activity and they tend to be higher in hypertensives (Buhler et al, 1980).

4. Vascular responses to exogenous catechols

Young hypertensives, with normal levels of plasma norepinephrine, have an increased pressor response to exogenous norepinephrine (Figure 5). Such enhanced vascular responsiveness was also seen with exogenous angiotensin, so the effect may be a non-specific heightened reactivity of vessels that are structually thicker. However, the first degree normotensive relatives of hypertensives were found to have an enhanced pressor reactivity to exogenous norepinephrine (Doyle and Fraser, 1961) so there may be other factors involved.

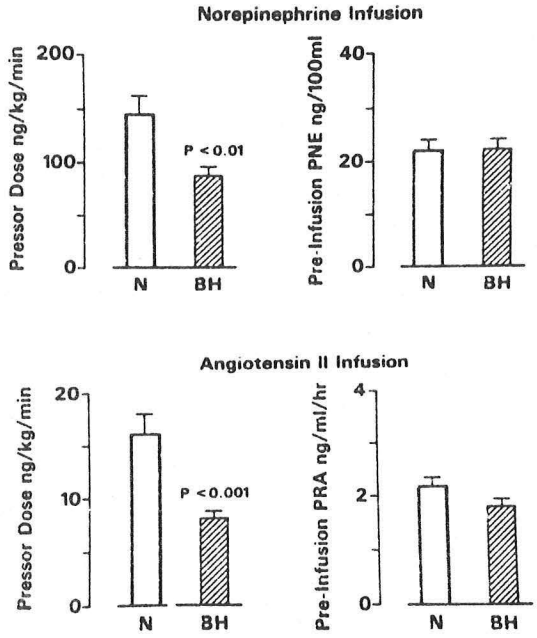

Figure 5 Pressor doses of norepinephrine or angiotensin II, and preinfusion plasma norepinephrine or renin levels in normal subjects (*N*) and patients with borderline hypertension (*BH*). The values are the mean ± SE. (From Meier A, Weidmann P, Grimm M, Keusch G, Gluck Z, Minder I, Ziegler WH: *Hypertension* 3:367, 1981.)

The arterial muscles of spontaneously hypertensive rats display increased sensitivity to norepinephrine which may reflect altered membrane potential electrogenesis, in turn triggered by a trophic factor of the sympathetic nervous system (Hermsmeyer et al, 1982)

5. Animal studies

Rats may develop hypertension in response to stress as a protection against more immediately bothersome consequences of the stress. When the blood pressure of rats was raised, they decreased their avoidance response to noxious stimuli by a baroreceptor-mediated reduction in cerebral arousal (Dworkin et al, 1979).

Folkow has reviewed the large amount of experimental data, mainly on rats who spontaneously develop hypertension, that show, even before the pressure has become elevated, an enhanced central autonomic discharge after psychological stimuli (Folkow, 1982). He has proposed this sequence: stress → genetically determined autonomic nervous overactivity → intermittent rise in blood pressure → structural changes in resistance vessels → permanent hypertension. Abboud (1982) has summarized the evidence for a role of the sympathetic nervous system in hypertension in both animals and man.

C. Genetic Predisposition (Table 6)

1. Familial correlations

Until large surveys showed that there was no distinct boundary between normotensive and hypertensive people, hypertension was believed to be inherited in a simple Mendelian manner. Blood pressure is now known to aggregate in families in a manner consistent with a polygenic mode of inheritance, which accounts for about half of the population variance (Havlick and Feinleib, 1982). Similarities between relatives resemble such continuous traits as height rather than such discrete traits as blood groups.

Table 6
Familial Correlations for Blood Pressure

Relationship	Correlations for Blood Pressure
Adult siblings	0.20
Parents and offspring	0.15
Identical twins	0.55
Fraternal twins	0.25
Spouses	Insignificant
Adopted children	None

2. Inherited differences

As noted previously, normotensive relatives of hypertensive people often have greater vascular reactions to stress and exogenous catechols which may be heightened by high sodium intake. The most likely specific defect involves sodium transport, either in the kidney alone or in other cells as well.

a. Renal sodium excretion

In numerous strains of rats that develop hypertension when given a high sodium diet, the fault appears to be in their kidneys. Transplantation experiments show that the blood pressure follows the kidney: when a kidney from a normotensive (R) donor is transplanted to a hypertensive (S) host, the blood pressure of the host falls to normal (Figure 6). And the reverse also is true: when a hypertensive (S) donor's kidney is transplanted into a normotensive (R) host, the host becomes hypertensive. Bianchi, et al (1975) showed that the kidney from a rat from a young susceptible donor, removed prior to the onset of hypertension, would cause a normotensive rat to develop hypertension. Sodium retention accompanied the rise in the pressure.

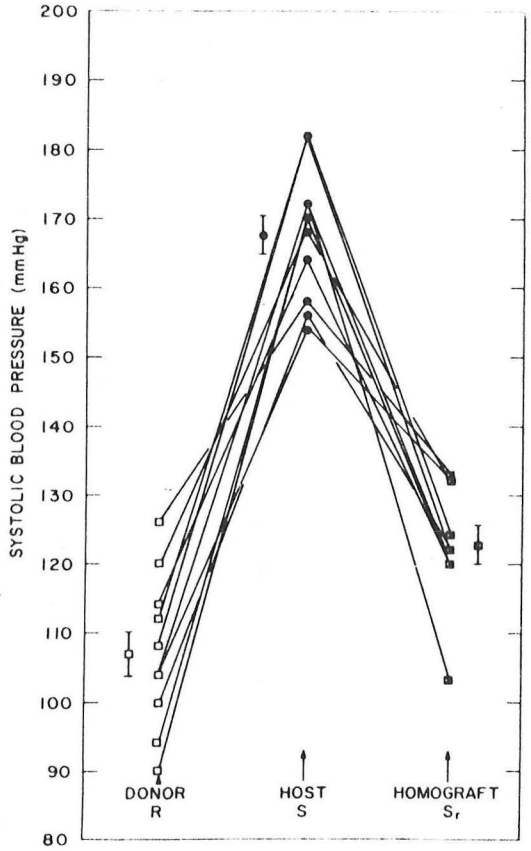

Figure 6 The effect of transplanting a "normotensive" kidney from the *Donor R* (resistant) rats to hypertensive *Host S* (sensitive) rats. The resultant blood pressure levels at a median time of 17 weeks after surgery are on the *right*. The mean blood pressure ± SE is indicated for each group. (Reproduced from Dahl LK, Heine M. *Circ Res 36*:692, 1975.)

Human studies such as this might be feasible if human donor recipients could be followed long enough. (A recent paper reports that human kidney recipients seldom develop much hypertension despite high dietary sodium intake (Kalbfleish et al, 1982), but the donors were almost certainly normotensive, thereby providing further evidence that both a high sodium intake and a genetic defect are needed.) Lacking such evidence, we must depend on much less direct evidence of renal retention of sodium. This revolves around the theoretical construct of Guyton and others that, in simple terms, states: for the blood pressure to become and remain elevated, the kidneys must re-set their normal

tendency to excrete sodium and water whenever the pressure begins to rise. There is no evidence for an inherited mechanism for the reset "pressure-natriuresis" relation. As noted earlier, many believe this re-setting could reflect a sympathetically mediated renal efferent arteriolar vasoconstriction, which would decrease renal blood blow (RBF) more than glomerular filtration (GFR), thereby increasing the fraction of blood that is filtered, leading to an increase in peritubular oncotic pressure and an increase in sodium reabsorption.

Once hypertension develops the excretion of sodium loads is not inhibited but rather is faster than normal, i.e. exaggerated natriuresis. Some of the normotensive children of hypertensive parents have an exaggerated rate of sodium excretion (Wiggins, et al, 1978). But, as we shall see, this may arise secondary to the underlying defect in renal sodium excretion.

b. Sodium movement across cell membranes

Though there is no direct evidence for an inherited defect in renal sodium excretion, there is an increasing body of evidence that one or more of the mechanisms controlling sodium movement across cell membranes may be defective in hypertensives and in some of their normotensive children.

The extracellular concentration of sodium is 140 mmol/L, whereas the intracellular concentration is 7 to 10 mmol/L. There is normally a steady leak of sodium into the cell and of potassium out. This passive influx of sodium into cells is continually compensated for by active mechanisms which extrude sodium against the concentration gradient. At least 6 separate mechanisms for sodium transport have been identified in human red blood cells, the most easily studied cell membrane (Toteson, 1981). Four of these are shown schematically in Figure 7. The most active and physiologically important mechanism is the energy-requiring sodium-potassium pump that extrudes 3 intracellular sodium ions in exchange for 2 extracellular potassium ions. This Na-K pump obtains its energy from the hydrolysis of ATP by the activity of Na,K- ATPase and is selectively inhibited by ouabain.

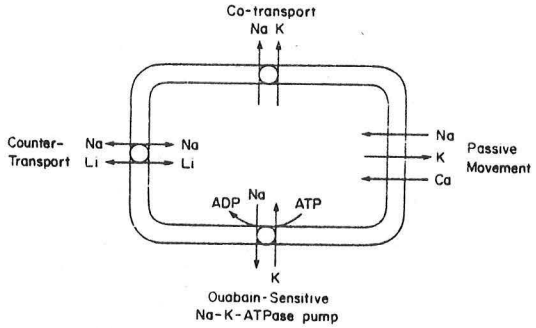

Figure 7 A schematic representation of four sodium transport mechanisms that have been demonstrated in red blood cells.

Studies on all of these transport mechanisms have been performed. Garay and Meyer measured the co-tranport (flux) of labelled sodium and potassium across red cells that have been treated to raise their sodium and lower their potassium content. The net Na/K flux ratio was lower in red cells of patients with primary (essential) hypertension than in normotensive subjects (Figure 8). The ratio was not lower in patients with secondary forms of hypertension, so the decrease does not simply follow the rise in blood pressure. Of great interest, half of the normotensive children of hypertensive parents had a low ratio. Subsequently, this lab has reported a pattern of abnormal Na/K flux in normotensive children that fits beautifully with a single autosomal dominant type of inheritance (Table 7). They have also found the same defect in red cells of 3 varieties of genetically hypertensive rats, including young animals before their blood pressure becomes elevated (DeMendonca et al, 1980).

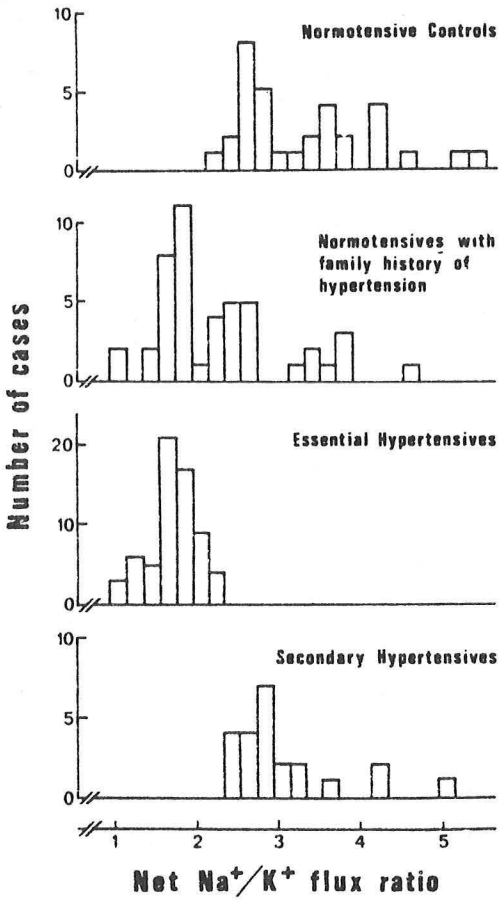

Figure 8 Histograms of erythrocyte sodium-potassium net flux ratios in normotensive controls with normotensive parents, young normotensive subjects with hypertensive parents, subjects with essential hypertension, and subjects with secondary hypertension and normotensive parents. The distribution of the patients with essential hypertension is distinctly different from that of the normotensive controls and the patients with secondary hypertension. The young normotensive subjects with hypertensive parents seem to be equally distributed among the two populations (From Garay RP, Elghozi J-L, Dagher G, Meyer P: *N Engl J Med 302*:769, 1980.)

Table 7
Abnormal Erythrocyte Na^+/K^+ Flux Test in Normotensive Children of Normotensive or Hypertensive Parents[a]

	Parents' Blood Pressure		
	Both Normotensive	One Hypertensive	Both Hypertensive
Number of children	86	97	19
Number with + test	3	52	14
Per cent + test	3.5%	53.6%	73.6%
Per cent expected with autosomal dominant gene	0	50.0%	75.0%

[a]Data from Meyer et al, 1981

II. The Presence of Increased Intracellular Sodium

The abnormal flux ratio shown in Figure 8 reflects a decreased efflux of sodium out of the red cells. Long before this finding, cells from hypertensives had been shown to contain more sodium than normal cells. The first such report came from work done in the old Southwestern shacks by Louis Tobian and John Binion (1952), who found an increased sodium concentration in the renal arteries obtained from hypertensive patients at necropsy.

In 1960, Losse et al first reported that RBC's from hypertensives had an increased sodium concentration. Since then, white blood cells have also been shown to have an increased sodium content (Edmundson et al, 1975).

Table 8
Transport Defects in Red and White Blood Cells Reported in Patients with Hypertension

Measurement	Defect	Reference
Red Blood Cells		
Intracellular Na content	Increased	Losse et al., 1960
Passive Na influx	Increased	Wessels et al., 1967
Na efflux (ouabain-resistant)	Increased	Postnov et al., 1977
Na-K cotransport	Decreased efflux of Na[a]	Garay and Meyer, 1979
Na-Li countertransport	Increased rate[a]	Canessa et al., 1980
K-Na countertransport	Increased K efflux	Adragna et al., 1981a
Na-K pump (ouabain-sensitive) (Rb uptake)	Increased Rb influx[a]	Woods et al., 1981
White Blood Cells		
Intracellular Na content	Increased	Edmundson et al., 1975
Na-K pump (ouabain-sensitive)	Decreased Na^+ efflux	Edmundson et al., 1975
Membrane permeability	Increased	Forrester and Alleyne, 1981

[a] Defect also found in normotensive relatives of patients with primary hypertension.

Numerous studies have examined sodium and potassium transport in both red and white cells of patients with primary hypertension. At present, defects have been shown in all 4 mechanisms shown in Figure 7 (Table 8). Of even greater interest, various defects have been demonstrated in red cells from at least some normotensive children of hypertensive parents, including:

--decreased Na-K cotransport (Meyer et al, 1981)
--an increased rate of Na-Li countertransport (Canessa et al, 1980; Clegg et al, 1982; Woods et al, 1982)
--an increased uptake of rubidium-86, which is handled similarly to potassium but is easier to measure (Woods et al, 1981)
--an increased sodium-22 influx (Henningsen and Nelson, 1981)
--a decreased total sodium efflux rate constant in leucocytes, owing to reduced ouabain-sensitive sodium pump activity Heagerty et al, 1982)

The literature as to which of these or other pathways is involved in primary hypertension continues to expand. As of now, there are conflicting data from different labs and no one defect has been uniformly found in all with primary hypertension. Some have not found clear differences in one or another of these in vitro measurements of sodium transport (Swarts et al, 1981; Ibsen et al, 1982), whereas a reduced Na,K- ATPase activity has also been found in obese Pima Indians (Klimes et al, 1982). Moreover, patients with primary hypertension may turn out to have different defects and the temptation to lump them under one mechanism may be inappropriate. Those hypertensives with a positive family history of hypertension and those without such a family history may be different: an increased sodium-dependent lithium efflux on average in hypertensives with a +FH but a normal lithium efflux in those with a negative FH has been reported from three labs (Cusi et al, 1981; Canali et al, 1981; Clegg et al, 1982). At this time, the presence on the average of increased intracellular sodium content of RBC's and WBC's from hypertensives seems well substantiated. And there are strong data that the passive influx of sodium is increased (Birks and Langlois, 1982) and that the active pumping of sodium out of cells through the ouabain-sensitive Na,K- ATPase pump mechanism is decreased (Edmundson, 1975).

Such defects in red and white cells are presumably only markers or, more hopefully, reflections of similar defects in vascular smooth muscle cells. The old data of Tobian and Binion showed more sodium in vascular tissue. Whether it gets there by defects in one or another of these transport systems remains unknown.

III. The Presumed Role of Natriuretic Hormone

The story now needs to go back to pick up links in another causal chain for which there is considerable experimental evidence. This involves the same Na,K- ATPase active pump mechanism but invokes an acquired inhibition of its activity by a humoral factor.

The first suggestion that the blood of hypertensives contains a humoral substance which can raise the blood pressure in normotensives seems to have been made by Dahl and co-workers (Dahl et al, 1967). When they connected a salt-sensitive (S) rat by parabiosis to a nephrectomized salt-resistant (R) rat, the blood pressure of the R rat slowly rose (Dahl et al, 1967). This rise was interpreted to reflect the presence of a "hypertensinogenic" circulating substance made in the salt-sensitive rat in an attempt to increase its sodium excretion. i.e. a natriuretic factor (Dahl et al, 1969). In 1972, Mizukoshi and Michelakis reported that the injection of 15 microliters of plasma from hypertensive patients increased the vascular reactivity of rats to norepinephrine and angiotensin, whereas plasma from normotensives did not.

The first direct evidence that plasma from hypertensives contains a natriuretic hormone came from Haddy and Overbeck's observations published in 1976 on various animal models of hypertension which involved sodium expansion. They found reduced activity of Na,K- ATPase and sodium pump activities in both cardiac and vascular smooth muscle of animals made hypertensive by volume expansion, which they interpreted to reflect the action of a circulating ouabain-like agent. When cardiac glycosides are given to normals, cardiac contractility increases and the blood pressure rises (particularly if a diuresis cannot occur) and peripheral vessels constrict (DeMots et al, 1978). The Na,K- ATPase enzyme is inhibited by ouabain, so the finding of reduced Na,K- ATPase activity was logically assumed to reflect an ouabain-like substance that appeared after volume expansion and which could be responsible for the hypertension.*

The search for a natriuretic hormone goes back at least to 1961 when de Wardener et al were trying to explain the sodium diuresis after saline loading in dogs. Welt et al in 1964 found evidence for such a factor in patients with renal failure and numerous attempts have been made to isolate and identify such a "third factor." Recently investigators at the Bowman-Gray School of Medicine have found a material in plasma of volume-expanded dogs (Plunkett et al, 1982) and hypertensive monkeys (Gruber et al, 1981) which binds specifically to antibodies against digoxin and inhibits Na,K- ATPase activity. They have called the yet to be isolated substance "endoxin."

1. The source for natriuretic hormone

Assuming that such a hormone exists, its source appears to be from the brain. In rats, selective lesions in the periventricular tissue of the anterior and ventral portion of the third ventricle (AV3V) will

*A decreased concentration of potassium will also inhibit the Na,K-ATPase pump, providing another biochemical mechanism for the hypertensive potential of hypokalemia or reduced ECF potassium content.

prevent the development of volume-expansion hypertension and the inhibition of Na,K- ATPase that accompanies the hypertension (Songu-Mize et al, 1982).

A few people with hypothalamic lesions have been reported to have "essential hypernatremia" which could be caused by an inability to excrete sodium from a lack of natriuretic hormone (Ross and Christie, 1969).

There is also evidence for a natriuretic hormone which comes from cardiac atrial tissue which could be involved in the natriuretic response to an increase in central blood volume, as after water immersion (Epstein, 1978). This hormone has a direct natriuretic effect upon the kidney into which it is injected (Keeler, 1982).

2. The actions of natriuretic hormone(s)

The physiologic effects of a natriuretic hormone are thought to reflects its inhibition of the Na,K- ATPase enzyme which is responsible for the active extrusion of sodium from cells. In the renal tubule, this would reduce the reabsorption of sodium, giving rise to a natriuresis. Thereby both the initial volume expansion would be reversed and there would be an exaggerated natriuresis after a sodium load.

In the vascular smooth muscle, the inhibition of Na,K- ATPase would, as we have seen, increase intracellular sodium concentration. There is now fairly good evidence that the plasma of hypertensive patients contains an inhibitor of Na,K- ATPase that will increase the sodium concentration of normal red and white blood cells to the same level as found in hypertensive cells (de Wardener and MacGregor, 1982). Perhaps the most convincing evicence for such a circulating inhibitor of Na,K- ATPase in patients with primary hypertension comes from Blaustein's lab (Hamlyn et al, 1982)(Figures 9 and 10).

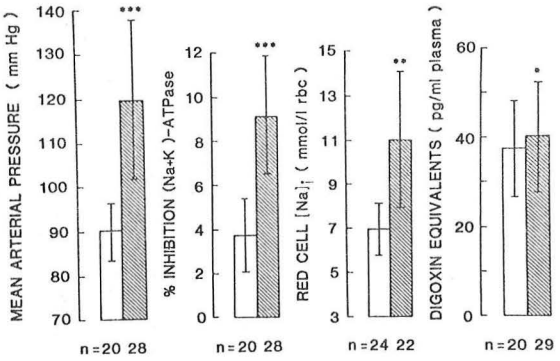

Fig. 9: Mean arterial blood pressure, % inhibition of Na,K- ATPase by plasma, intracellular RBC sodium content and plasma digoxin equivalents in normotensives (open bars) and hypertensives (hatched bars)(From: Hamlyn et al, 1982).

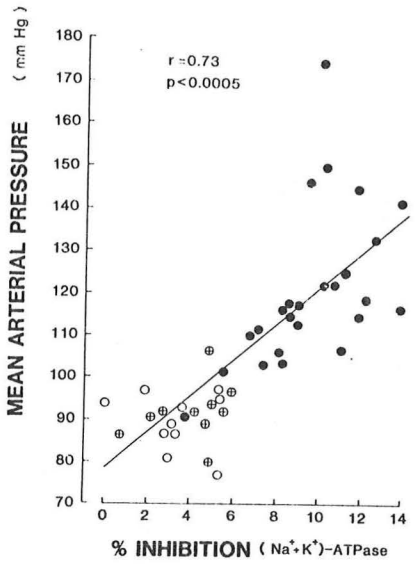

Fig. 10: Relationship between mean arterial blood pressure and the % inhibition of Na,K- ATPase by plasma samples from normotensives (open circle) and hypertensives (closed circles). The filled circles and crossed-circles correspond to 6 hour integrated samples; open circles, single samples from normotensives (From: Hamlyn et al, 1982).

Additional evidence includes these observations:

1. When white blood cells from normotensive subjects were incubated in serum obtained from patients with primary hypertension, the cells developed the same impairment in sodium efflux rate that is found in the white cells of hypertensive patients (Poston et al, 1981b). These results show that at the least this defect in sodium transport need not be inherited since it can be induced by exposure to serum from hypertensive patients.

2. The greatest impairment of the sodium efflux rate from white blood cells was seen in those hypertensives with the lowest plasma renin levels (Edmundson and MacGregor, 1981). Such patients are likely the most volume expanded and would be expected to have the highest level of natriuretic hormone.

3. When the white cells of normotensives were incubated with fractions of urine obtained after volume expansion by saline infusion, which would be expected to increase the levels of natriuretic hormone, the mean Na-efflux rate was significantly depressed (Poston et al, 1982).

4. When hypertensives were treated with diuretics and presumably had their need for natriuretic hormone diminished by the shrinkage of fluid volume, the Na-K transport defects in their white cells were corrected (Poston et al, 1981a).

To recapitulate, according to the hypothesis proposed by de Wardener and MacGregor (1980), "Essential hypertension in man is due to an inherited variability in the ability of the kidney to eliminate sodium. This variability becomes increasingly obvious the greater the sodium intake. The difficulty in eliminating sodium increases the concentration of a circulating sodium-transport inhibitor. This substance affects sodium transport across cell membranes. In the kidney, it adjusts urinary sodium excretion so that sodium balance is near that of normal subjects on the same intake of sodium, thus making it difficult to demonstrate an increase in extracellular fluid volume. In the arteriole, it causes a rise in intracellular sodium concentration, which in turn raises the intracellular calcium concentration and thus increases vascular reactivity."

IV. An Integrated Scheme for the Pathogenesis of Primary Hypertension

The last part of de Wardener and MacGregor's summation brings us to the last part of the "sodium-transport" hypothesis. So far, we have seen how either an inherited defect in sodium transport or an acquired defect (via renal sodium retention → expanded vascular volume → natriuretic hormone → inhibition of Na, K-ATPase) could result in an increased intracellular sodium and, further, that such an increased intracellular sodium has been found in cells from many patients with primary hypertension.

A. The increase in intracellular calcium

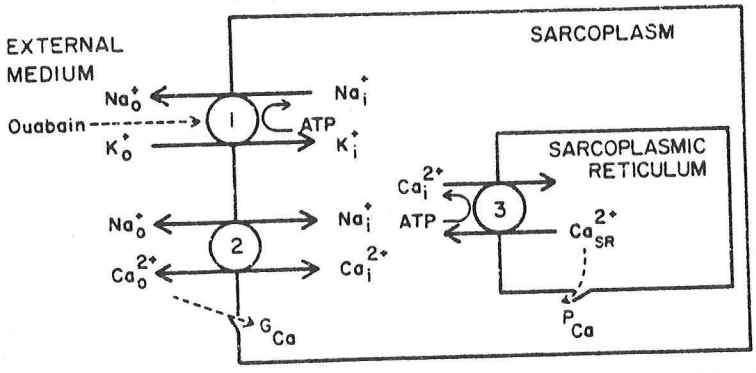

Figure 11 A diagram of compartmentalization of Ca in muscle fibers. Main pathways and transport systems for Na and Ca are shown: ① ATP-dependent, ouabain-sensitive Na-K exchange pump; ② sarcolemmal Na-Ca exchange mechanism, ③ sarcoplasmic reticulum (SR) ATP-dependent Ca pump. Most of the entering Ca is assumed to come through voltage-sensitive conductance (G_{Ca}) channels associated with action potentials. P_{Ca} indicates the mechanism that releases Ca from the sarcoplasmic reticulum. (From Blaustin MP: in Zumkley H and Losse H (eds), *Intracellular Electrolytes and Arterial Hypertension*. Georg Thieme Verlag, New York, 1980.)

The most likely mechanism for the translation of an increased intracellular sodium into a hypertensinogenic force was first hypothesized by Mordecai Blaustein (1977). The concept proposes that the increased intracellular sodium would directly increase intracellular calcium, through a number of pathways (Figure 11):

1. An inhibition of Na-K exchange pumps, shown as 1 in Figure 11, would depolarize the muscle fiber and thereby increase Ca entry through voltage-sensitive Ca channels, shown at the bottom left of Figure 11.

2. An increase in intracellular sodium will result in a smaller Na electrochemical gradient between the sarcoplasm and external medium, thereby decreasing the extrusion of Ca from the cell via the Na-Ca exchange which derives its energy from this gradient, shown as 2 in Figure 11.

3. An increase in intracellular sodium in the presynaptic terminals of sympathetic neurons promotes Ca-dependent norepinephrine release. The norepinephrine releases Ca from intracellular stores, shown as 3 in Figure 11.

In whatever manner the higher intracellular sodium acts to increase the concentration of intracellular calcium, a very small rise in intracellular sodium can, by theoretical calculations, be shown to cause enough of a rise in intracellular calcium to increase the resting tone of vascular smooth muscle by about 50% (Blaustein, 1977).

Other mechanisms may be responsible for higher intracellular calcium in hypertension: 1) the inner side of RBC membranes from hypertensive patients was found to have a reduced capacity to bind Ca, thereby increasing free Ca within the cell (Orlov and Postnov, 1982); 2) passive Ca influx was increased; and 3) ATP-dependent calcium extrusion was reduced in red cells from SHR rats (Devynck et al, 1981).

In summary, vascular smooth muscle intracellular calcium is likely elevated in primary hypertension. Since intracellular calcium directly controls vascular contraction and relaxation, the connection to hypertension is obvious. Increased vascular tone and reactivity are likely responsible for much of the increased total peripheral vascular resistance (TPR) that is the primary mechanism of sustained hypertension.

B. An integrated scheme (Figure 12)

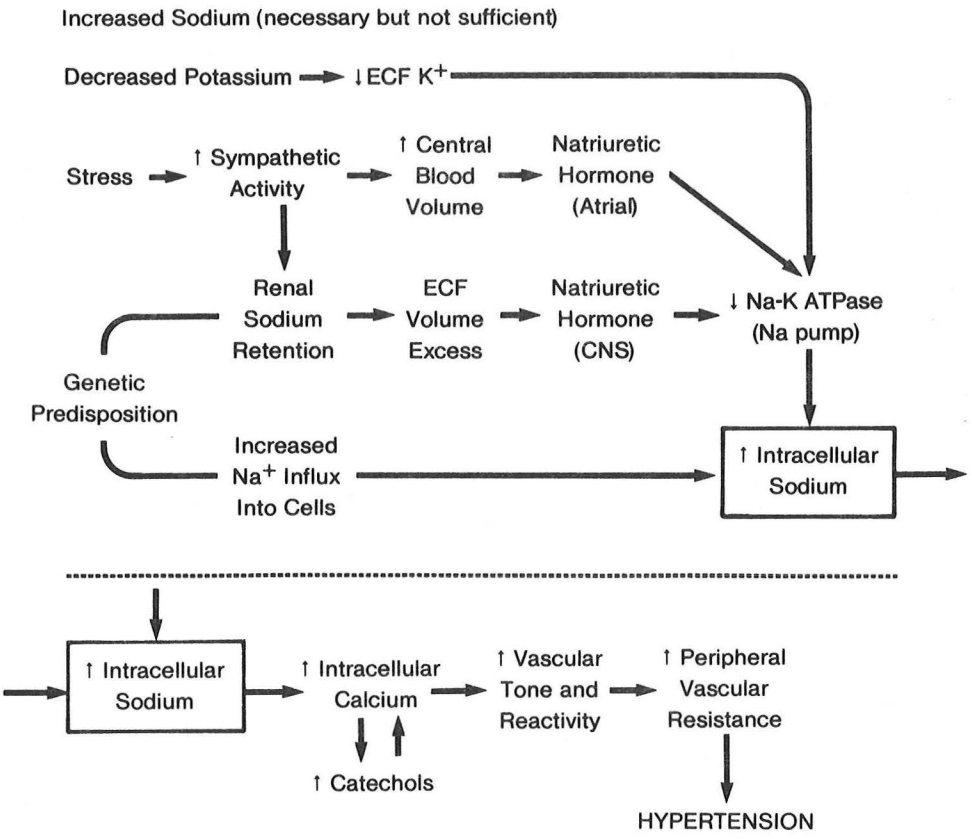

Fig 12: An integrated scheme for the pathogenesis of primary (essential) hypertension.

Figure 12 attempts to put all of the preceding (and a bit more that hasn't been directly covered) into an integrated scheme. As shown, the rise in intracellular sodium could arise from an inhibition of Na-K-ATPase, in turn mediated by deficient dietary potassium or one or another natriuretic hormones, with or without the intercession of stress-induced activation of the sympathetic nervous system. And, as another path to the higher cellular sodium, an inherited defect in sodium influx could act directly, to the exclusion of all of the above.

Which of these (or other) mechanisms turns out to be responsible remains to be seen. Presumably none would be effective without the concomitant presence of "excess" dietary sodium, a necessary but not in itself significant part of the pathogenetic scheme.

For completeness, I will refer to some recent papers by David McCarron and co-workers who find reduced levels of plasma ionized calcium and decreased dietary intake of calcium in hypertensive animals and people along with increased urinary calcium excretion (McCarron, 1982; McCarron et al, 1982). The increased calcium excretion could

reflect an increased dietary sodium intake (Breslau et al, 1982) but the remainder of McCarron's data cannot very easily be put into the scheme here proposed. However, with the assumption that a reduced calcium intake may somehow be involved, caution is advised in curtailing dietary sources of calcium such as milk and cheese in an attempt to reduce dietary sodium intake.

V. The Sites of Action of Antihypertensive Agents

It's easy to show that the various antihypertensive agents work on one or another portion of the integrated scheme. Of particular interest is the pivotal role of intracellular calcium, suggesting a major potential for calcium-entry blockers in the treatment of hypertension. They lower the blood pressure, significantly more in hypertensives than in normotensives by causing greater vasodilation, whereas the vasodilator response to nitroprusside was reduced in hypertensives (Robinson et al, 1982). Such a selective response further suggests a role for increased intracellular calcium in the etiology of hypertension.

VI. The Potential for Prevention

Far better than life-long drug treatment, even if it were specifically aimed at a fundamental defect, would be prevention. The various non-drug modalities which may lower an elevated blood pressure--weight loss, sodium restriction, relief of stress by one one or another relaxation techniques--may prevent the pressure from rising in the first place. No adequate trials of prevention have been done and none may be feasible, but all of these modalities are safe and practical and therefore their use should be encouraged, particularly in those with a positive family history of hypertension.

Though prevention and correction of obesity and stress may be worthwhile, they would be more difficult to accomplish than a general reduction in dietary sodium intake. In view of the evidence portrayed in this presentation the need to proceed with sodium restriction, even in the absence of definitive proof that it will prevent hypertension, seems to me to be appropriate and rather urgent, particularly in view of the ever more widespread use of life-long drug therapy. Here the words of Geoffrey Rose (1981) seem appropriate:

"As doctors we are trained to feel responsible for patients--that is, to care for the sick; and from that position accepting responsibility for those with major risk factors is not too difficult a transition. They are almost patients. A general practitioner, say, makes a routine measurement of a man's blood pressure and finds it raised. Thereafter both the man and the doctor will say that he "suffers" from high blood pressure. He walked in a healthy man but he walks out a patient, and his new-found status is confirmed by the giving and receiving of tablets. An inappropriate label has been accepted because both public and profession feel that if the man were not a patient the doctor would have no business treating him. In reality the care of the symptomless hypertensive person is preventive medicine, not therapeutics."

"If a preventive measure exposes many people to a small risk, then the harm it does may readily--as in the case of clofibrate--outweigh the benefits since these are received by relatively few....We may thus be unable to identify that small level of harm to individuals from long-term intervention that would be sufficient to make that line of prevention unprofitable or even harmful. Consequently we cannot accept long-term mass preventive medicine" (Rose, 1981).

The widespread adoption of a diet moderately restricted in sodium, to a level around 2000 mg (88 mmol) per day should be practical. The increasing availability of processed foods lower in sodium content and the increasing labelling of foods so that the consumer can know what is in the container will certainly help. It may not achieve the goal of preventing hypertension, but it can do no harm. As Rose indicates: "All the life-saving benefits achieved by current antihypertensive treatment might be equalled by a downward shift of the whole blood pressure distribution in the population by a mere 2-3 mm Hg. The benefits from a mass approach in which everybody receives a small benefit may be unexpectedly large" (Rose, 1981). Therefore, the moderation of sodium intake should be encouraged, certainly for therapy and, I believe, for prevention as well.

The author wishes to acknowledge the help of Elizabeth L. Narkiewicz, Alfred E. Carnegie, M.D. and Donna Odle.

References

1. Abboud FM: The sympathetic system in hypertension. Hypertension 4(suppl II):II208-II225, 1982.

2. Ayachi S: Increased dietary calcium lowers blood pressure in the spontaneously hypertensive rat. Metabolism 28:1234-1238, 1979.

3. Beard TC, Cooke HM, Gray WR, Barge R: Randomised controlled trial of a no-added-sodium diet for mild hypertension. Lancet 2:455-458, 1982.

4. Beretta-Piccoli C, Davies DL, Boddy K, et al: Relation of arterial pressure with body sodium, body potassium and plasma potassium in essential hypertension. Clin. Sci. 63:257-270, 1982.

5. Bianchi G, Baer PG, Fox U, et al: Changes in renin, water balance, and sodium balance during development of high pressure in genetically hypertensive rats. Circ. Res. 36&37(suppl I):I-153-I-161, 1975.

6. Birks RL, Langlois S: Ouabain-insensitive net sodium influx in erythrocytes of normotensive and essential hypertensive humans. Proc. R. Soc. Lond. 216:53-69, 1982.

7. Blaustein MP: Sodium ions, calcium ions, blood presusre regulation, and hypertension: a reassessment and a hypothesis. Am. J. Physiol. 232(3):C165-C173, 1977.

8. Breslau NA, McGuire JL, Zerwekh JE, Pak CYC: The role of dietary sodium on renal excretion and intestinal absorption of calcium and on vitamin D metabolism. J. Clin. Endocrinol. Metab. 55: 369-373, 1982.

9. Buhler FR, Amann FW, Bolli P, et al: Elevated adrenaline and increased α-adrenoceptor-mediated vasoconstriction in essential hypertension. J. Cardiovasc. Pharmacol. 4:S134-S138, 1982.

10. Bulpitt CJ: Sodium excess or potassium lack as a cause of hypertension: a discussion paper. J. R. Soc. Med. 74:896-900, 1981.

11. Campese VM, Romoff MS, Levitan D, et al: Abnormal relationship between sodium intake and sympathetic nervous system activity in salt-sensitive patients with essential hypertension. Kidney Int. 21:371-378, 1982.

12. Canali M, Borghi L, Sani E, et al: Increased erythrocyte lithium-sodium countertransport in essential hypertension: its relationship to family history of hypertension. Clin. Sci. 61:13s-15s, 1981.

13. Canessa M, Adragna N, Solomon HS, et al: Increased sodium-lithium countertransport in red cells of patients with essential hypertension. N. Engl. J. Med. 302:772-776, 1980.

14. Carney S, Morgan T, Wilson M, et al: Sodium restriction and thiazide diuretics in the treatment of hypertension. Med. J. Aust. 1:803-807, 1975.

15. Cassel J: Hypertension and cardiovascular disease in migrants: A potential source of clues? Int. J. Epidemiol. 3:204-206, 1974.

16. Chapman CB, Gibbons TB: The diet and hypertension. Medicine 29:29-69, 1949.

17. Clegg G, Morgan DB, Davidson C: The heterogeneity of essential hypertension. Lancet 2:891-894, 1982.

18. Conn JW: The mechanism of acclimization to heat. Advances Intern. Med. 3:373-393, 1949.

19. Cusi D, Barlassina L, Ferrandi M, et al: Familial aggregation of cation transport abnormalities and essential hypertension. Clin. Exp. Hypertens. 3:871-884, 1981.

20. Dahl LK: Salt and hypertension. Am. J. Clin. Nutr. 25:231-244, 1972.

21. Dahl LK, Knudsen KD, Heine M, Leitl G: Effects of chronic excess salt ingestion. J. Exp. Med. 126:687-699, 1967

22. Dahl LK, Heine M: Primary role of renal homografts in setting chronic blood pressure levels in rats. Circ. Res. 36:692-696, 1975.

23. Dahl LK, Knudsen KD, Iwai J: Humoral transmission of hypertension: Evidence from parabiosis. Circ. Res. 24-25(Suppl 1):I21-I33, 1969.

24. Dahl LK, Leitl G, Heine M: Influence of dietary potassium and sodium/potassium molar ratios on the development of salt hypertension. J. Exp. Med. 136:318-330, 1972.

25. DeMendonca M, Grichois M, Garay RP, et al: Abnormal net Na^+ and K^+ fluxes in erythrocytes of three varieties of genetically hypertensive rats. Proc. Natl. Acad. Sci 77:4283-4286, 1980.

26. DeMots H, Rahimtoola SH, McAnulty JH, Porter GA: Effects of ouabain on coronary and systemic vascular resistance and myocardial oxygen consumption in patients without heart failure. Am. J. Cardiol. 41:88-93, 1978.

27. Denton D: Hypertension: A malady of civilization in Sambhi MP (ed.) Systemic Effects of Antihypertensive Agents, New York: Stratton, 1976, pg. 577.

28. Devynck M, Pernollet M, Nunez A, Meyer P: Analysis of calcium handling in erythrocyte membranes of genetically hypertensive rats. Hypertension 3:397-403, 1981.

29. de Wardener HE and MacGregor GA: Dahl's hypothesis that a saluretic substance may be responsible for a sustained rise in arterial pressure: Its possible role in essential hypertension. Kidney Int. 18:1-9, 1980.

30. de Wardener HE, MacGregor GA: The natriuretic hormone and essential hypertension. Lancet 1:1450-1454, 1982.

31. Doyle AE, Fraser JRE: Essential hypertension and inheritance of vascular reactivity. Lancet 2:509, 1961.

32. Dworkin BR, Filewich RJ, Miller NE, Craigmyle N, Pickering TG: Baroreceptor activation reduces reactivity to noxious stimulation: implications for hypertension. Science 205:1299-1301, 1979.

33. Dyer AR, Stamler J, Shekelle RB, Schoenberger J: The relationship of education to blood pressure. Circulation 54:987-992, 1976.

34. Edmondson RPS, MacGregor GA: Leucocyte cation transport in essential hypertension: its relation to the renin-angiotensin system. Brit. Med. J. 282:1267-1269, 1981.

35. Edmondson RPS, Thomas RD, Hilton PJ, et al: Abnormal leucocyte composition and sodium transport in essential hypertension. Lancet 1:1003-1005, 1975.

36. Epstein M: Renal effects of head-out water immersion in man: Implications for an understanding of volume homeostasis. Physiol. Rev. 58:530-581, 1978.

37. Falkner B, Onesti G, Angelakos ET, et al: Cardiovascular response to mental stress in normal adolescents with hypertensive parents. Hypertension 1:23-30, 1979.

38. Falkner B, Onesti G, Hayes P: The role of sodium in essential hypertension in genetically hypertensive adolescents in Onesti G and Kim KE (eds) Hypertension in the Young and the Old, New York: Grune and Stratton, 1981, pg 29-35.

39. Folkow B: Physiological aspects of primary hypertension. Physiol. Rev. 348-504, 1982.

40. Fregly MS: Salt and social behavior in Kare MR, Fregly MJ, Bernard RA (eds) Biological and Behavioral Aspects of Salt Intake, New York: Academic Press, 1980, pg 5-11.

41. Fujita T, Henry WL, Bartter FC, et al: Factors influencing blood pressure in salt-sensitive patients with hypertension. Am. J. Med. 69:334-343, 1980.

42. Garay RP, Meyer P: A new test showing abnormal net Na^+ and K^+ fluxes in erythrocytes of essential hypertensive patients. Lancet 1:349-353, 1979.

43. Gentry WD, Chesney AP, Gary HE, et al: Habitual anger-coping styles: 1. Effect on mean blood pressure and risk for essential hypertension. Psyschosom. Med. 44:195-202, 1982.

44. Goldstein DS: Plasma norepinephrine in essential hypertension. Hypertension 3:48-52, 1981.

45. Gruber KA, Rudel LL, Bullock BC: Increased circulating levels of an endogenous digoxin-like factor in hypertensive monkeys. Hypertension 4:348-354, 1982.

46. Haddy FJ, Overbeck HW: The role of humoral agents in volume expanded hypertension. Life Sci. 19:935-948, 1976.

47. Hamlyn JM, Ringel R, Schaeffer J, et al: A circulating inhibitor of (Na+K)-ATPase associated with essential hypertension. Nature (in press).

48. Havlik RJ, Feinleib, M: Epidemiology and genetics of hypertension. Hypertension 4(supp III):III121-III127, 1982.

49. Heagerty AM, Milner M, Bing RF, et al: Leucocyte membrane sodium transport in normotensive populations: Dissociation of abnormalities of sodium efflux from raised blood-pressure. Lancet 2:894-896, 1982.

50. Henningsen NC, Nelson D: Net influx and efflux of ^{22}Na in erythrocytes from normotensive offspring of patients with essential hypertension. Acta. Med. Scand. 210:85-91, 1981.

51. Henningsen NC, Mattson S, Nosslin B, et al: Abnormal whole-body and cellular (erythrocytes) turnover of $^{22}Na^+$ in normotensive relatives of probands with established essential hypertension. Clin Sci. 57:321S-234S, 1979.

52. Hermsmeyer K, Abel PW, Trapani AJ: Norepinephrine sensitivity and membrane potentials of caudal arterial muscle in DOCA-salt, Dahl, and SHR hypertension in the rat. Hypertension 4(suppl II): II49-II51, 1982.

53. Hollenberg NK: Set point for sodium homeostasis: Surfeit, deficit, and their implications. Kidney Int. 17:423-429, 1980.

54. Hollenberg NK, Borucki LJ, Adams DF: The renal vasculature in early essential hypertension: Evidence for a pathogenetic role. Medicine 57:167-178, 1978.

55. Hollenberg NK, Williams GH, Adams DF: Essential hypertension: Abnormal renal vascular and endocrine responses to a mild psycholgical stimulus. Hypertension 3:11-17, 1981.

56. Holly JMP, Goodwin FJ, Evans SJW, et al: Re-analysis of data in two Lancet papers on the effect of dietary sodium and potassium on blood pressure. Lancet 2:1384-1387, 1981.

57. Ibsen KK, Jensen HE, Wieth JO, Funder J: Essential hypertension: Sodium-lithium countertransport in erythrocytes from patients and from children having one hypertensive parent. Hypertension 4: 703-709, 1982.

58. Iimura O, Kijima T, Kikuchi K, et al: Studies on the hypotensive effect of high potassium intake in patients with essential hypertension. Clin. Sci. 61:77s-80s, 1981.

59. Kalbfleisch JH, Herbert LA, Lemann J, et al: Habitual excessive dietary salt intake and blood pressure levels in renal transplant recipients. Am J. Med. 73:205-210, 1982.

60. Kaplan NM: Clinical Hypertension, 3rd edition, Baltimore, Williams and Wilkins, 1982, pg 108-110.

61. Keller R: Atrial natriuretic factor has a direct, prostaglandin-independent action on kidneys. Can. J. Physiol. Pharmacol. 60: 1078-1082, 1972.

62. Kempner W: Treatment of hypertensive vascular disease with rice diet. Am. J. Med. 4:545-577, 1948.

63. Klimes I, Nagulesparan M, Unger RH, et al: Reduced Na^+,K^+-ATPase activity in intact red cells and isolated membranes from obese man. J. Clin. Endocrinol. Metab. 54:721-724, 1982.

64. Lever AF, Beretta-Piccoli C, Brown JJ, et al: Sodium and potassium in essential hypertension. Brit. Med. J. 283:463-468, 1981.

65. Losse H, Wehmeyer H, Wessels F: The water and electrolyte content of erythrocytes in arterial hypertension. Klin. Wochenschr. 38:393-395, 1960.

67. MacGregor GA, Markandu ND, Best FE, et al: Double-blind randomised crossover trial of moderate sodium restriction in essential hypertension. Lancet 1:351-355, 1982.

68. Magnani B, Ambrosioni E, Agosta R, Racco F: Comparison of the effects of pharmacological therapy and a low-sodium diet on mild hypertension. Clin. Sci. Mol. Med. 51:625s-626s, 1976.

69. McCarron DA: Low serum concentrations of ionized calcium in patients with hypertension. N. Engl. J. Med. 307:226-228, 1982.

70. McCarron DA, Henry HJ, Morris CD: Human nutrition and blood pressure regulation: An integrated approach. Hypertension 4(suppl III):III2-III13, 1982.

71. McCarron DA, Morris CD, Cole C: Dietary calcium in human hypertension. Science 217:267-269, 1982.

72. McCrory WW, Klein AA, Rosenthal RA: Blood pressure, heart rate, and plasma catecholamines in normal and hypertensive children and their siblings at rest and after standing. Hypertension 4:507-513, 1982.

73. Meier A, Weidmann P, Grimm M, et al: Pressor factors and cardiovascular pressor responsiveness in borderline hypertension. Hypertension 3:367-372, 1981.

74. Meneely GR, Battarbee HD: High sodium-low potassium environment and hypertension. Am. J. Cardiol. 38:768-785, 1976.

75. Meyer P, Garay RP, Nazaret C, et al: Inheritance of abnormal erythrocyte cation transport in essential hypertension. Brit. Med. J. 282:1114-1117, 1981.

76. Mizukoshi H, Michelakis AM: Evidence for the existence of a sensitizing factor to pressor agents in plasma of hypertensive patients. J. Clin. Endocrinol. Metab. 34:1016-1024, 1072.

77. Morgan T O, Myers JB: Hypertension treated by sodium restriction. Med. J. Aust. 2:396-397, 1981.

78. Morgan T, Adam W, Gillies A, et al: Hypertension treated by salt restriction. Lancet 1:227-230, 1978.

79. Nadeau JH, Fraser J, Robertson D, Wood AJJ: Increased sodium intake increases sensitivity to catecholamines through alteration in receptor density. Clin. Res. 28:240A, 1980.

80. Oliver WJ, Cohen EL, Neel JV: Blood pressure, sodium intake, and sodium related hormones in the Yanomamo Indians, a "no-salt" culture. Circulation 52:146-151, 1975.

81. Orlov SN, Postnov YV: Ca^{2+} binding and membrane fluidity in essential and renal hypertension. Clin. Sci. 63:281-285, 1982.

82. Page, LB: Hypertension and atherosclerosis in primitive and acculturating societies in Hunt JC (ed) Hypertension Update, Bloomfield: HLS Press, 1979, pg 1-12.

83. Page LB, Damon A, Moellering RC: Antecedents of cardiovascular disease in six Solomon Islands societies. Circulation 49:1132-1146, 1972.

84. Parijs J, Joosens JV, Van der Linden L, et al: Moderate sodium restriction and diuretics in the treatment of hypertension. Am. Heart J. 85:22-34, 1973.

85. Pickering G: Salt intake and essention hypertension. Cardiovasc. Reviews and Reports 1:13-17, 1980.

86. Plunkett WC, Hutchins PM, Gruber KA, Buckalew VM: Evidence for a vascular sensitizing factor in plasma of saline-loaded dogs. Hypertension 4:581-589, 1982.

87. Postnov YV, Orlov SN, Schevchenko A, Adler AM: Altered sodium permeability, calcium binding and Na-K-ATPase activity in the red cell membrane in essential hypertension. Pflugers Arch. 371: 263-269, 1977.

88. Poston L, Jones RB, Richardson PJ, Hilton PJ: The effect of anti-hypertensive therapy on abnormal leucocyte transport in essential hypertension. Clin. Exp. Hypertens. 3:693-701, 1981a.

89. Poston L, Sewell RB, Wilkinson SP, et al: Evidence for a circulating sodium transport inhibitor in essential hypertension. Brit. Med. J. 282:847-849, 1981b.

90. Poston L, Wilkinson S, Sewell RB, Williams R: Sodium transport during the natriuresis of volume expansion; a study using peripheral blood leucocytes. Clin. Sci. 63:243-249, 1982.

91. Robertson D, Shand DG, Hollifield JW, et al: Alterations in the responses of the sympathetic nervous system and renin in borderline hypertension. Hypertension 1:118-124, 1979.

92. Robinson BF, Dobbs RJ, Bayley S: Response of forearm resistance vessels to verapamil and sodium nitroprusside in normotensive and hypertensive men: evidence for a functional abnormality of vascular smooth muscle in primary hypertension. Clin. Sci. 63:33-42, 1982.

93. Rose G: Strategy of prevention: lessons from cardiovascular disease. Brit. Med. J. 282:1847-1851, 1981.

94. Ross EJ, Christie SBM: Hypernatremia. Medicine 48:441-470, 1969.

95. Sever PS, Gordon D, Peart WS, Beighton P: Blood-pressure and its correlates in urban and tribal Africa. Lancet 2:60-63, 1980.

96. Songu-Mize E, Bealer SL, Caldwell RW: Effect of AV3V lesions on development of DOCA-salt hypertension and vascular Na^+-pump activity. Hypertension 4:575-580, 1982.

97. Sullivan JM, Ratts TE, Taylor JC, et al: Hemodynamic effects of dietary sodium in man. Hypertension 2:506-514, 1980.

98. Swarts HGP, Bonting SL, de Pont JHHM, et al: Cation fluxes and Na^+-K^+-activated ATPase activity in erythrocytes of patients with essential hypertension. Hypertension 3:641-649, 1981.

99. Tobian L, Binion T: Tissue cations and water in arterial hypertension. Circulation 5:754-758, 1952.

100. Tosteson DC: Cation countertransport and cotransport in human red cells. Federation Proceedings 40:1429-1433, 1981.

101. Trowell HC: Salt and hypertension. Lancet 2:88, 1980.

102. Veith I: The yellow emperor's classic in internal medicine (translated from Huang Ti Nei Ching Su Wen, 2600 BC), Berkeley, University of California Press, 1966.

103. Wessels VF, Junge-Hulsing G, Losse H: Passive sodium influx into red blood cells. Z. Kreislaufforschung 56:374-379, 1967.

104. Wiggins RC, Basar I, Slater JDH: Effect of arterial pressure and inheritance on the sodium excretory capacity of normal young men. Clin. Sci. Mol. Med. 54:639-647, 1978.

105. Woods KL, Beevers DG, West M: Familial abnormality of erythrocyte cation transport in essential hypertension. Brit. Med. J. 282: 1136-1137, 1981.

106. Woods JM, Falk RJ, Pittman AW, et al: Increased red-cell sodium-lithium countertransport in normotensive sons of hypertensive parents. N. Engl. J. Med. 306:593-595, 1982.