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dissertation entitled

Blood Pressure Sensitivity to Dietary Sodium

in Zimbabwean Men

presented by

Jacob Mufunda

has been accepted towards fulfillment
of the requirements for

Ph.D. degree in Physiology

Major professor

Date November 16, 1988

BLOOD PRESSURE SENSITIVITY TO DIETARY SODIUM IN ZIMBABWEAN MEN

By

Jacob Mufunda

A DISSERTATION

Submitted to
Michigan State University
in partial fulfilment of the requirements
for the degree of

DOCTOR OF PHILOSOPHY

Department of Physiology

1988

ABSTRACT

BLOOD PRESSURE SENSITIVITY TO DIETARY SODIUM IN ZIMBABWEAN MEN

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We tested the hypothesis that young Zimbabwean black men would significantly increase mean arterial pressure on dietary sodium loading as do American blacks. We measured blood pressures, 24 hour urinary sodium, potassium, and calcium and plasma hormones of 19 young normotensive black men, mean age, 19.4 years, on control diet, and after 4 days of 10 mEq/day sodium and 800 mEq/day sodium diet. Our results showed that these young men significantly increased systolic blood pressure and decreased diastolic blood pressure and did not significantly change their mean arterial pressure from the 10 mEq/day sodium to the 800 mEq/day diet sodium diet. These young Zimbabwean men did not therefore exhibit a similar response to the American blacks who significantly increased systolic pressure, diastolic pressure and mean arterial pressure on similar dietary changes. Our subjects were able to suppress renin angiotensin system as assessed by plasma AII and aldosterone. Because we observed pressor sensitivity in an older group of Zimbabwean men, we propose that in African blacks, the pressor sensitivity to sodium is a function of age.

Our working hypothesis for the study in the older population of Zimbabwean men, was urban men would exhibit larger mean arterial

pressure increases than rural men on acute dietary sodium loading and that this pressor sensitivity is mediated by different hormonal responses. Twenty rural men with a mean age of 39 years and age matched urban men were studied using an identical protocol to the one used for the young men described above. Both groups of men significantly increased systolic and mean arterial pressure but did not significantly alter diastolic pressure from the low salt to the high salt diet. Sodium pressor sensitivity is not responsible for the observed threefold increase in the hypertension prevalence associated with urbanization. The data also suggests that on low salt diet rural men use a reduction in ANP as an alternate pathway for sodium conservation rather than aldosterone which is different from urban men who used aldosterone.

In conclusion, young Zimbabwean men are resistant to the pressor effects of sodium and hence are unlike American blacks. There was no unusual hormone response to explain this sodium resistance. Sodium pressor sensitivity appears to be a function of age because older urban and rural men were sensitive to the pressor effects of sodium. Both groups of men were able to suppress plasma aldosterone concentration on sodium loading. Rural men use suppression of ANP to conserve sodium whereas urban men use aldosterone. The mechanism for this use of ANP to conserve sodium is not known.

This thesis work is especially dedicated to my wife, Eustina who sacrificed her own professional committments in order to accompany me for most of the time of my studies and to my daughter, Tendai Michelle for just being there, and also to my mother VaSango, my father the late Jona Mukuvisi and to my brothers and sisters: Tinos, Vitalis, Esther, Agnes, Bernadette, Thomas, Enock, Gabriel, Emilia, the late Joseph and finally Rosemary.

ACKNOWLEDGEMENTS

So many people contributed to this thesis work for which I am very grateful. First and foremost I would like to thank my thesis advisor, Dr. Harvey V. Sparks, for everything. He helped me collect data and analyse it. I would like to extend my special thanks to the rest of my thesis guidance committee, Dr John Chimoskey, Dr. Gregory Fink, Dr. Robert Stephenson, Dr. Patrick Dillon, and Dr. Kenneth Schwartz for their constructive criticism and thorough scrutiny of my progress.

I am grateful to members in the Faculty of Medicine at the University of Zimbabwe, namely, Dr. Pedzisai Vengesa, Dr. Cephas Musabayane, and Dr John Matenga, for their technical support and encouragent and Sister Sheila Mukumba of the School of Nursing for technical help.

I also extend my thanks to Dr. Gloria Cobb and Sr. Kathy McCarty who arranged for board for both the researchers and the subjects while Jaison prepared the food for subjects at Chidamoyo Mission hospital. I would like to thank Mr. Blair who allowed us to use the university dormitories for our subjects. Mrs. Kodzwa, Mrs. Mhembere, Ms. Schlenke and Mrs. Makamure facilitated the preparation and serving of food to our research subjects for which I am grateful.

I am grateful to Dr. Rudy Bernard and Karen Mooney for allowing me access to their laboratory and helping me with the ANP radioimmunoassay. Dr. Gregory Fink and Corrinni Powloski have provided extensive help for doing the aldosterone assay without which this work would be inadequate, for which I am very grateful.

I am indebted to Dr. Harvey V. Sparks's laboratory group of which I have been a member for the past four years, comprised of Dr. Lana Kaiser, Greogory D. Romig, Dr. Roger Wangler, Dr. Mark Gorman, Dr. Sharon Kelly, Dr. William Frantz, Dr. Robert Pittman, Dr. M-X He, Elizabeth Meade, and Carol Hall for their help and the day to day assessment of the progress of my laboratory analysis. Greg was particularly instrumental in teaching me how to use the computer and Lana helped with the preparation of the thesis drafts for which I am very grateful.

Finally, I would like to express great appreciation to Esther Brenke for extensive secretarial work towards this manuscript.

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INTRODUCTION

This introduction has been divided into three broad sections. The first section is brief and deals with the definition of hypertension and how it is a medical problem. The second section reviews the literature on the epidemiology of hypertension. This section highlights the absence of hypertension in traditional populations before the onset of western influence in different population groups. An attempt is made to relate westernization and urbanization to the emergence of hypertension in these previously normotensive traditional societies. Studies in the same geographical regions are described together to stress the global nature of this relationship. The third and final section deals with factors which may be involved in the development of hypertension in societies where it was initially rare.

Hypertension as a Health Problem

The distribution of arterial pressure in a population may be viewed as normal or bimodal (Master et al., 1943; Rocella et al., 1987). When arterial pressure is viewed as normally distributed, the highest 5% of arterial pressures are regarded as hypertension. When arterial pressure is viewed as a bimodal distribution, hypertension has its own distribution which is shifted to the right of the blood pressure distribution curve of normotensive subjects in the same population (Hamilton and Pickering, 1954).

Normotension has been defined by the World Health Organization (WHO) as arterial pressure values from a single sitting or recumbent position of less than 140 mmHg systolic pressure, and less than 90 mmHg diastolic pressure (phase 5 Korotkov sounds), (WHO Tech. Rep., 1958). This definition ignores the possible influence of age, sex, and weight. To ignore them is a possible shortfall of this definition, because arterial pressure is positively correlated with weight and age in most industrial societies (Intersalt, 1988). However, the lack of correlations of age with blood pressure in some nonwesternized societies may provide justification.

The WHO defines hypertension as a single blood pressure (sitting or recumbent) equal to or exceeding 160/95 mmHg. Individuals with blood pressure measurements between normotensive and hypertensive and less than 30 years old are to be "viewed with suspicion" (WHO Tech. Rep., 1958). This intermediate group is said to have "borderline hypertension." Blood pressure of individuals with borderline hypertension is labile, and these individuals are characterized by increased sympathetic activity, increased plasma renin, increased cardiac output and a greater increase in blood pressure with age (Robertson et al., 1979).

In clinical situations, age is often considered in the definition of hypertension. When age is incorporated into the definition of hypertension, hypertension is blood pressure greater than or equal to 160/95 mmHg for ages 17-60 years and greater than or equal to 175/95 for ages 60 years and older (Julius et al. 1982). Normotension is a blood pressure less than 140/90 mmHg between 17 and 40 years, less than 150/90 for ages 41 to 60 years, and less than 160/90 for ages over 60

years. In age ranges 17 to 60 blood pressure is fairly stable. Again, borderline hypertension is the blood pressure reading between normotension and hypertension (Julius et al. 1982).

Hypertension is classified as essential (primary) or secondary. Ninety five percent of hypertension is considered essential, the cause of which is unknown. Secondary hypertension is the form in which the cause can be identified. Secondary hypertension is therefore, potentially curable.

Hypertension is a major medical problem in many societies. The prevalence of hypertension, which is the percentage of people in any area at a given time with that problem, is not uniform. American blacks have a higher prevalence of hypertension than American whites (Saunders and Bancroft, 1941; Moser et al., 1959; Prineas and Gillum, 1985; Stamler et al., 1976). Hypertension related mortality is also higher in American blacks than whites (Gillum and Prineas, 1985).

Hypertension prevalence increases with westernization and urbanization. Westernization refers to exposure and consequent acquisition of western culture in both rural and urban environment. Urbanization in this context, refers to the changes in way of life which accompany moving into a city environment. Since in developing countries, large numbers of people are migrating to urban areas, the influence of urbanization on the development of hypertension is of significance.

Epidemiology of Blood Pressure

Absence of hypertension in traditional cultures:

First, I will review the studies reported before 1965 when hypertension was virtually absent in unwesternized native populations. At this time both American blacks and whites and European whites had prevalences of hypertension greater than 10%. In addition, blood pressure was known to increase with age (Page, 1982). However, in some population groups hypertension was rare and blood pressure did not increase with age. To illustrate this very interesting blood pressure pattern, reports from both Africa and South America are briefly described below.

African Studies

In 1929 Donnison reported blood pressure measurements in the natives of South Kenya. Blood pressure measurements were made in 1,000 healthy subjects, ranging in age from 15 years to 60 years old. About 100 subjects were studied in each decade of age. Blood pressure significantly decreased from 123/82 mmHg at 15 years to 105/67 mmHg with over 60 years of age. This decline of blood pressure with age was quite different from that reported in western societies. At this time it was unclear whether Donnison's data were applicable for all unwesternized population groups. No obvious explanation was forthcoming for this unusual blood pressure pattern.

Williams failed to detect hypertension in his 1941 blood pressure survey on 394 pastoral and agricultural Ugandan natives. In both men

and women blood pressure did not increase with age after 30 years of age. This study demonstrated the paucity of hypertension in African natives living traditionally.

Kaminer et al. (1960) confirmed Donnison's original observations by demonstrating the absence of hypertension and failure of blood pressure to increase with age in individuals whose lifestyles had not been changed by western influence. They studied the blood pressure of Bushmen, a traditionally nomadic tribe of the Kalahari Desert. The subjects comprised 78 nomadic adults and 21 adult farm workers and prisoners. Average blood pressure of the nomads was 108/66 mmHg for men and 112/70 mmHg for women, respectively. The blood pressure was significantly higher for the male farm laborers and prisoner than the male nomads. The researchers proposed that increased stress resulting from more contact with western living conditions may have been responsible for the higher pressures observed in in the farm laborers and prisoners compared to their nomadic counterparts.

Traditional Africans were not the only ones who did not develop high blood pressure with age. Similar findings were observed in the Aborigines of Australia and China, Indians of Alaska (Page, 1982) and native populations of South America and Pacific Islands. The South American and Pacific Islands findings are detailed below.

South American and Pacific Island Studies

In 1961 Maddocks studied Fijians in Gau Island. Altogether, 1,546 men and 1,536 women (99 % of the population) were studied. In another Pacific Island, Gilbert Island. Blood pressure was measured in all adults in 14 out of 16 villages. Average blood pressures were 128/79

mmHg at 20 years and 132/79 mmHg at 70 years of age. Hypertension was not recorded in this population. In addition, blood pressure did not increase with age. This study differs from the above mentioned reports in that nearly the entire population was studied. It is sometimes difficult to correct for environmental, geographical and social factors which are known to influence blood pressure. Therefore, a complete population study is ideal. These data suggest hypertension was not a problem in these populations.

Oliver et al. (1975) studied the Yanomamo Indians of Northern Brazil and Southern Venezuela, a "no-salt" culture. Average systolic pressure between ages of 10 and 20 years was 105 mmHg. Average systolic pressure was 105 mmHg at 50 years of age. Diastolic pressure did not significantly change between the two age ranges. The very low salt intake (less than 2 mEq sodium/day) in this population was a surprising finding. The pressor effect of sodium and its role in hypertension had already been highlighted (Dahl et al., 1962). Circumstantially, the reported low dietary sodium intake in these subjects was a logical explanation for the absence of hypertension. Thus, both the low salt intake and the absence of the stresses of western cultural influences have been suggested as possible explanations for the low blood pressures of people living in traditional nonwestern cultures.

Lot Page et al. (1974) examined 2,586 people aged 15 years and above, in 6 tribal societies living in 6 Solomon Islands. These subjects were subject to varying levels of western influence. Estimates of this influence were made from the duration and intensity of contact with western culture, entry into money economy, medical care, level of formal education and dietary change. Systolic blood pressure

increased with age only in females from 3 population groups with a relatively high level of westernization. No significant systolic pressure changes with age were demonstrated in males. Diastolic pressure decreased with age in males from areas with low western acculturation levels. This study provided strong epidemiological evidence for the relationship between blood pressure and western influence.

As indicated earlier, Maddocks (1961) proposed that there can be two blood pressure distribution curves in any population. The first curve is a normal physiological curve which is present in every population.The second is an abnormal curve located above the normal curve. These two curves overlap. He proposed that pressures in the higher distribution are acquired usually as a result of stress, and represent hypertension. This abnormal curve was not yet present at the time of study of the native populations of Africa, the South Pacific islands and elsewhere, because these individuals had not yet been exposed to western influence: their pressure distributions are unimodal. That is, hypertension did not exist in these population groups as manifested by lack of the second curve or bimodal distribution typical of western societies. because they had not acquired the second curve.

Emergence of hypertension in traditional cultures

After 1960 numerous investigators reported significant incidence and prevalence of hypertension in populations previously at low risk. In addition, both systolic and diastolic pressure increased with age in these populations. The new pattern of high blood pressure was quite

similar to what was reported in both American blacks and whites. The following studies illustrate this new blood pressure pattern.

East African Studies

In 1965 Forsyth described a 1.1% prevalence of hypertension in a rural, mainland Tanzanian population. At the same time the prevalence of hypertension in Zanzibar, an island off the coast of Tanzania, was 4.9%. These two hypertension prevalences were in subjects from the same genetic population who lived in different environments. The prevalence of hypertension increased with age. This suggests that in this population blood pressure increased with age. In these two surveys, diastolic pressure greater than 100 mmHg was considered hypertension rather than the WHO level of 95 mmHg which is used in most surveys. Thus, Forsyth probably underestimated the actual prevalence of hypertension in this study. This study was one of the earliest to document increased hypertension prevalence with age in Africa. It was also interesting to notice the higher hypertension prevalence in the island population than inland population. There were no comments on these differences. It is possible that the greater western influence on the island than on the mainland contributed to higher hypertension prevalence on the Island.

A similar finding of increased blood pressure with age was reported by Parry (1969). The survey involved 1,500 men and 700 women aged 20 to 70 years who lived traditionally in Ethiopian highlands. While the prevalence of hypertension was not recorded average blood pressure increased with age. These data demonstrate a western blood pressure pattern which is quite different from that in the earlier stuies. No

explanation was given for the western pattern of blood pressure increase with age in this population, although this finding differs from earlier ones. However, Akinkugbe has pointed out that some rural Nigerians also have hypertension (see below).

It was not, however, until Shaper et al. (1968) emphasized the probable role of the environment in the development of hypertension in Africans that explanations were sought through longitudinal studies. Members of a traditionally nomadic Kenyan tribe, Samburu, were drafted into the Kenyan army. Lifestyle markedly changed, with adoption of western culture. For example, the army recruits were supplied with daily food rations that provided 15 grams of salt, compared to less than four grams per day in the traditional environment. Blood pressure in the army recruits significantly increased compared to the their counterparts still living traditionally. There was a positive correlation between the number of years spent in the army and the increase in both systolic and diastolic pressure. When grouped according to age, blood pressure in these subjects was much higher than that of their counterparts still leading a traditional nomadic life. It is unknown if the higher salt intake caused the enhanced blood pressure increase with age or if some other factor associated with joining the army is responsible.

Data from Shaper, Page et al., 1974, and Oliver et al., 1975 suggested that increased intake of sodium may be responsible for the observed increase in blood pressure with westernization. However, it may not be absolute sodium intake that is most closely related to blood pressure increase with urbanization. The dietary sodium/potassium ratio may be a better predictor of the increase in blood pressure associated

with urbanization (Poulter et al., 1984). This ratio has been shown to be positively correlated to blood pressure in both animal and human studies (Dahl et al., 1962; Intersalt, 1988).

Poulter et al. (1984) studied the Kenyan Luo subsistence farmers in their rural environment. They studied three hundred Luo who had migrated to the urban environment of Nairobi. The urban men were were identified by contact tracing using addresses obtained from the rural areas. The prevalence of hypertension was not reported, but average blood pressures were higher in the urban than in the rural traditional subjects. Spot urine collections from these subjects showed higher sodium/potassium ratio in the urban than rural population. While spot urine collections are not the best way to estimate electrolyte intake they may provide a rough guide.

West African Studies

The study of West Africans has been considered especially relevant to the understanding of hypertenssion in American blacks because West Africa is the primary source of the American blacks traced from the slave trade (Grim 1988). Akinkugbe and Ojo (1969) reported on the blood pressures of 2,000 rural and 2,000 urban Nigerian men and women. They studied approximately 200 subjects in each decade of life from 15 to 55 years of age. This study suggests that average blood pressure increased significantly with age in both environments and in both sexes, however, the increases were much higher in the urban than in the rural population. Prevalence of hypertension was not reported in this population study.

Southern African Studies

Seedat et al. (1983) studied members of the South African Zulu tribe who had migrated to the urban environment. From 1975 to 1976, 1,000 urban people were studied in a random house to house survey. Blood pressure increased with age in this population. They reported a prevalence of hypertension (WHO definition) of 25% in men and 27% in women. These investigators also surveyed 987 rural Zulu people. The prevalence of hypertension was lower for the rural group than for the urban group, 8.7% for men and and 10% for women. In these studies, blood pressure increased with age and the prevalence of hypertension was higher in urban than rural people. Interestingly, both hypertension prevalences, rural and urban, were higher in women than in men.

The hypertension prevalence was recently reported to be 24% in urban Zimbabwe (Intersalt, 1988). In June 1987, an informal survey of 1000 adults was performed in Chidamoyo, which is 200 miles from Harare, the capital of zimbabwe. The population was contacted through the medical personnel in the area, the local chief and party leaders. Rendezous places were selected. People came and gathered at these sites to have their blood pressures measured. All people older than 15 years were included in the study. Although the prevalence of hypertension was 7%, this survey must be regarded as informal because selection of the subjects was not completely random. It was biased by sself selection of those people who wanted to come to have their pressures measured.

3. Higher blood pressure in rural than urban people.

In some studies, blood pressure has been shown to be low in

unwesternised communities and not to increase with age. However, in all african studies urbanization has been associated with increased average pressures and a higher prevalence of hypertension. This effect of urbanization has not been found in North America and the Carribean Islands. Whether this difference in effect of urbanization between African and American based studies has relevance has not been critically evalated. North American blacks originated from West Africa during the slave trade. West Africa has a tropical climate which is hot and conducive to salt and sweat loss through high sweat production. Even with acclimatization, this increased body fluid loss is accompanied by sodium (Wilson, 1986). Enteric diseases leading to diarrhea were probably common. Furthermore, there is historical evidence that salt was in short supply in West Africa during the time of slavery. Given an environment which promoted sodium loss and in which sodium supply was scanty, it would make sense that these people developed sodium conservation mechanisms which are now genetically inherited. This thesis research in zimbabwe is relevant to the study of hypertension in American blacks. It is significant for this study that Zimbabwean Bantus and West African Bantus are of the same genetic stock.

Grim et al. (1988) propose that slavery represented an additional pressure for selection of those individuals with a propensity to save sodium. The poor public health conditions associated with slavery must have led to frequent enteric fluid losing infections. The West Africans who survived both the tropical climate and slavery must have had a phenomenally high sodium conservation ability. The assumption is that this increased ability to retain sodium became an inherited trait. The theory states that in this way the present day black American has a

gentic predisposition to enhanced sodium retention. The temperate North American climate is associated with minimal sweat sodium loss, enteric disease is minimal and salt is freely available. Presumably the combination of the high sodium intake and a tendency for sodium retention leads to increased body sodium which in turn leads to increased blood pressure (Grim, 1988).

Miall et al. (1962) studied 1,550 females and 1,130 males in urban and rural Jamaica. Two populations were defined geographically. The urban population was from Kingston the capital of Jamaica. The rural population was from an area 20 miles from Kingston. Members of the rural population were engaged in vegetable gardening and sold their products in the city and commuted between their rural home and the city. At all ages, from 15 to 75 years, the females from the rural area had significantly higher average pressures than females from the urban area. No explanation was proposed for the higher blood pressure in rural than in urban women. One could speculate that in the rural area, women are the primary source of income. In the urban areas it could be the men. Rural women could be more stressed and busy commuting to town to sell their products for a living whereas the urban women might be less economically active with their husbands doing most of the work. The higher pressure in rural women may be due to the greater stress in rural than urban women.

Kotchen and Kotchen (1978) investigated the geographic effect on racial blood pressure differences in American black and white adolescents. Blood pressure measurements were done on high school students from an urban area, Washington D.C., and a rural area, Bourbon County, Kentucky. Systolic pressure was higher in rural than urban

groups in both races. In the urban group, black males had a mean systolic pressure of 122 mmHg which was higher than 116 mm Hg in white males. Mean systolic pressure of black rural males (124 mmHg) was higher than 122 mm Hg in urban black males. Mean systolic blood pressure of rural black males and rural white males was the same. Systolic pressures for all groups of females were lower than for all groups of males in both rural and urban population. The systolic pressure of urban black females of 110 mmHg was lower than 115 mmHg in rural black females. Systolic blood pressure was 106 mmHg for urban white females and 114 mmHg for rural white females. Briefly, blood pressure was not different between races in the rural area. Systolic pressure was significantly higher in urban blacks than in urban whites. These observations suggest that environmental factors including geographic differences contribute to the racial blood pressure differences in adolescents. The higher blood pressure in rural than urban in this study contrasts with findings from studies in Africa.

The epidemiology of hypertension in the Bahamas was studied by Moser et al. (1959). Blood pressure was measured in 3,594 people. Blood pressure increased with age in this population. Mean blood pressure at 20 years of age was 122/77 mmHg in males and 120/75 mmHg in females. Mean blood pressure was 185/100 mmHg in males and 166/96 mmHg in females at 60 years of age. In this study, the prevalence of diastolic hypertension (greater than 100 mmHg) was 23% for females and 29% for males. The prevalence of systolic hypertension (greater than 150 mmHg) was 48% in males and 35% in females. These hypertension prevalence figures were higher than reported for whites in the U.S.A., but similar to the reported values for blacks in U.S.A., and in the U.S. Virgin

Islands. This suggested that the hypertension prevalence in blacks is higher than in whites regardless of area in the American continent and Carribean Islands or level of urbanization. The assumption here is the American continental blacks are more urbanized than those from the Carribean Islands.

Possible Explanations for urbanization related hypertension

The mechanisms proposed to explain the higher average pressures per age group and higher prevalence of essential hypertension in blacks than whites. These mechanisms include psychosocial stresses, higher sodium ingestion or a possible genetic predisposition to the pressor effects of dietary sodium, decreased dietary supplies of potassium, calcium, protein, fiber, and increases in dietary carbohydrate, magnesium, polyunsaturated fatty acids, and protein.

Psychosocial Stresses

Evidence from Animal Experiments

Friedman and Dahl (1963) reported significant increases in systolic pressure increases after 13 weeks of subjecting rats to aversive conditioning, in rats with a genetic susceptibility to experimental hypertension. This study suggested that experimentally induced stress can induce hypertension in susceptible individuals. Cessation of operant conditioning resulted in normalization of blood pressure in some but not all animals, implying heterogeneity in the response and possible role of sensitivity to this kind of stress induced hypertension. This study suggests that stress alone can induce both transient and permanent

hypertension in rats. Interaction of sodium and stress has been implicated in contributing to the higher hypertension prevalence in blacks than whites (Grim, 1988). The relevance of this interaction of sodium, stress and hypertension was examined by Anderson et al. (1983) who reported a study in dogs using operant conditioning schedules and intraarterial infusions of normal saline. Dogs that received either intraarterial infusions of saline or operant conditioning alone did not develop increase in systolic pressure. Dogs that received both saline infusion and operant conditioning simultaneously increased systolic pressure significantly. This study demonstrated that simultaneous administration of sodium chloride and stressful operant conditioning can induce increases in blood pressure.

Evidence for Stress in Humans

Harburg et al., in 1978, studied four areas in Detroit which were selected on the basis of widely varying social and stressful conditions. All areas were racially segregated. High stress areas were marked by low socioeconomic status, high population density, high crime rate, high residential mobility, and high incidence of marital breakups. Low stress areas were opposite. Blood pressures were highest in black high stress males. Blood pressures of blacks and whites in low stress areas were not different. For blacks, skin color was positively related to blood pressure. High stress black males had darker skin color than black middle class males. Black high stress men with darker skin color had the highest blood pressures of all the four groups. This study relates well to the animal stress studies above.

To examine the relationship between prevalence of hypertension and level of education, Dyer et al. (1986) investigated more than 40,000 employed Chicagoans. A significant inverse relationship was observed between the level of education and hypertension in all groups of white subjects. This inverse relationship could not be accounted for by differences in age, weight, or heart rate among the different education strata. Controlling for these variables did, however, lessen the association. Among blacks, a significant inverse relationship between blood pressure and level of education was evident for young males. There was no significant association between blood pressure and level of education in black females and older black males. This study indirectly suggests that stress and hypertension can be initiated by a low level of education. Low socioeconomic status that follows may contribute to high blood pressure development.

Light et al. (1985) noticed that exposure to competitive mental tasks significantly reduced the urinary sodium and fluid excreted by young men who had either borderline hypertension or one or two hypertensive parents. In this group who at high risk of developing hypertension, the degree of sodium retention was directly related to the magnitude of the heart rate increase during stress. The magnitude of increase in heart rate is measure of sympathetic nervous system activation in these subjects. Sympathetic nervous system activation causes both increased heart rate and increased renin release which leads to increased body sodium retention. This finding is significant because it shows that these young men at high risk of developing hypertension exhibit an abnormal sympathetic nervous system response which may lead to salt retention. This abnormal response could the predisposing factor

to the development of hypertension. The reduction in fluid and sodium excretion would lead to expanded extracellular fluid volume. The resultant increase in blood volume could lead to increase cardiac output and systolic blood pressure (Luft et al., 1979). In this high risk group the degree of retention was directly related to the magnitude of heart rate increase during stress.

The potential significance of stress in the etiology of hypertension is probably best indicated by a study by Simmons et al. (1986). They contacted a blood pressure survey in rural and urban Malawi. The average sodium intake is 72 mEq/day in urban population and 37 mEq in the rural population. The average systolic pressure at 15 years of age is 117 mmHg for rural and 125 mmHg for urban. At 60 years of age urban systolic pressure is 150 mmHg compared to rural blood pressure of 125 mm Hg. The urban area is Lilongwe, the rapidly growing capital city of Malawi. The rural population is from the area around Lilongwe. The blood pressure increase with age in this urban population with a medium to low sodium intake is a surprizing finding. The authors proposed the following explanation for blood pressure increase with age in this population is stress associated with urbanization. Henry and colleagues (1988) computed evidence from a survey of mortality due to hypertension in cities with various growth rates. A high growth rate such as that in Lilongwe implies inadequate housing, and a need for facilities such as schools, hospitals, and public transportation together with immigrants unused to the demands of urban life. The change and lack of resources in the rapidly growing urban environment stress the people who attempt to adjust them. Increased stress may increase the prevalence of hypertension in this population which would otherwise be expected to

have low blood pressure based on the low sodium intakes alone. Of course this is just a hypothesis at this time.

Sodium and Hypertension

Epidemiological Evidence

The dietary sodium hypothesis of causation of hypertension continues to generate controversy. Abundant evidence suggests that high sodium intake is causally related to hypertension, at least under some circumstances (Dahl et al., 1962). Epidemiological studies reviewed by Page (1982) and recently reported (Intersalt, 1988) demonstrate a strong positive correlation between blood pressure and dietary sodium intake.

In the 1982 review, all population groups in more than 20 independent surveys were classified on the basis of sodium intake. Three groups of populations were recognized: low, medium and high sodium populations. The low sodium populations consumed less than 100 mEq sodium/day. The medium sodium populations consumed between 100 and 200 mEq sodium/day; whereas the high sodium groups consumed in excess of 200 mEq of sodium/day. The low sodium populations have lower blood pressure than either medium or high sodium populations. The low sodium low blood pressure populations are best typified by the Yanomamo Indians of Northern Brazil and Southern Venezuela. Their sodium intake is less than 2 mEq/day. In this population, blood pressure does not increase with age and hypertension is rare. The high sodium high blood pressure groups are best exemplified by the native inhabitants of Northern Japan. The sodium intake in this poulation is in excess of 400 mEq/day. Blood pressure increases with age and hypertension is very common. In fact,

the inhabitants of Northern Japan have the highest hypertensive stroke rates world wide.

The majority of population groups are classified as medium sodium medium blood pressure with sodium intake ranging between 100 and 200 mEq sodium/day. It is this medium sodium group that has been most extensively studied. Studies in individual cultural groups in this medium population have failed to show a positive correlation between blood pressure and either dietary sodium intake or the ratio of sodium to potassium in he diet. The narrow range of sodium intake in a culture has been given as a possible explanation for the absence of correlation between pressure and sodium intake.

There have been a few exceptions to this absence of positive correlation between blood pressure and sodium intake. Kesteloot et al. (1988) reported a positive correlation between urinary sodium excretion and blood pressure in the inhabitants of China. A negative correlation between blood pressure and potassium was present in this study. The researchers suggested that success in obtaining a positive correlation between blood pressure and sodium relates to the other dietary factors of the Chinese who eat little vegetables and fruits. Consequently they have low urinary potassium excretion. This combination of dietary electrolytes leads to a high urinary sodium/potassium ratio which is known to be positively correlated with high blood pressure.

In summary, the epidemiological studies suggest a causative relationship between extremely high sodium intake and high blood pressure and hypertension. They also suggest that if sodium intake is between 100 and 200 other causative factors become significant.

Animal Studies

The above epidemiological studies have not provided strong evidence for a direct role for dietary sodium chloride in the development of essential hypertension. An animal model of hypertension that closely resembles sodium dependent human essential hypertension had not been developed until Dahl et al. produced a genetic strain of rats that is sensitive to sodium. Dahl et al. (1962) clearly demonstrated the genetic predisposition for the development of salt induced hypertension in normotensive Sprague Dawley (SD) rats. These investigators first demonstrated that intraperitoneal triiodothyronine (T3) injections enhanced blood pressure increase in the same SD rats. The animals that responded to T3 by highest increase in blood pressure were mated together. These mated sensitive rats produced offspring which after weaning received intraperitoneal T3. The siblings that responded with high blood pressure were mated together to produce the third generation of sensitive rats. The third generation of rats were more sensitive to T3 than the parents. SD rats that did not respond to T3 by increasing pressure were called resistant. The resistant rats were mated together. The siblings of the resistant rats were tested for sensitivity using T3 and those that were resistant mated to produce offspring that were more resistant to T3. This process of inbreeding produced offspring that were either more or sensitive and more resistant than the parents. The Dahl sensitive (S) exhibited increased blood pressure when subjected to 8% sodium chloride diet whereas the Dahl resistant (R) did not. It was not just the absolute amounts of sodium chloride that influenced blood pressure. When the Dahl S rats were fed a fixed sodium chloride intake

but with increasing amounts of potassium, they showed less increase in blood pressure dependent on the dose of potassium chloride. This influence of blood pressure by potassium and sodium is often expressed as sodium/potassium ratio. This molar ratio is calculated from 24 hour urinary excretion or intake of sodium and potassium. The sodium/potassium ratio has been shown to be positively correlated to blood pressure in both animal and human studies (Intersalt, 1988).

The sensitive rats were sensitive to to both T3 and high sodium chloride diet. This sensitivity to both stimuli of hypertension suggests a possible common pathway for all stimuli of hypertension in susceptible animals. The Dahl S hypertension model has been well characterized. The animal has been shown to be unable to excrete a sodium load effectively. This inability to excrete sodium appears to be localized in the kidney. Bilateral nephrectomy in these Dahl S rats and transplantation of normal SD rat donor kidneys prevents the development of hypertension on 8% sodium diet. Transplantation of donor Dahl S rats kidneys to recipient Dahl R rats increases blood pressure in the Dahl R rats on 8% sodium diet. The lesion appears to be humoral because parabiosis of Dahl S with Dahl R on high sodium diet increases blood pressure in both animals. However the precise cellular mechanism or nature of this humoral factor has not been well worked out.

Human Studies

The ideal method of studying human hypertension would be to do all the protocols followed on the Dahl S rats, but this is impossible for obvious reasons. As a result three populations are available for study

of essential hypertension pathophysiology: i.e., normotensives, hypertensives and borderline hypertensives. There are advantages and disadvantages to the study of any of these groups. It would seem logical to study hypertensives because they are the individuals with the problem. If the object is therapy, hypertensives are the right group to study. The major problem in studying hypertensives is that an abnormality in a hypertensive individual may be either a case or a result of the hypertension.

The study of normotensive subjects circumvents the latter problem, but the disadvantage is that normotensives may be the group that is "immune to hypertension" i.e. equivalent to Dahl R group of rats. Hence findings inthem may be misleading.

Investigations which have pursued individual variations in response to changes in sodium balance have led to the development of the concept of sodium sensitivity and sodium resistance (Falkner, 1988). As yet there is no uniform definition of sodium sensitivity or resistance. The criteria of sodium sensitivity or sodium resistance vary according to the design of the study. A decrease of mean arterial pressure by 10 mmHg following furosemide induced diuresis was used as sodium sensitivity by Weinberger et al. (1982). In a study of Skrabal et al. (1980), reduction of mean arterial pressure of 5 mmHg following a diet of reduced sodium intake was regarded as a sodium sensitive response. On the other hand, other studies have used an increase in mean arterial pressure following an oral or intravenous sodium load as evidence for sodium sensitivity. In addition to different methods of sodium challenge, these investigations vary in the conditions of the study, (for example, home hospital or research unit), the prestudy sodium

balance and the control of other dietary factors.

In this review, studies in normotensives are discussed first. A number of studies have been done on normotensive subjects to explore the mechanism of sodium related hypertension. Both acute and chronic dietary intervention studies have been done. Luft et al. (1979) studied seven black and seven white normotensive men on different levels of sodium intake. All subjects received 10 mEq sodium/day for 7 days. Daily 24 hr urinary excretion of sodium was measured for all the days. The subjects approached sodium balance after 3 days. After 3 days, the 24 hour sodium intake was the same as the 24 hour urinary sodium excretion. The dietary sodium was sequentially increased to 300, 600, 800, 1,200, and 1,500 mEq/day for 4 days on each diet. All the subjects were studied on the 10 and 300 mEq/day diets. Three whites and 3 blacks were studied on the 600 and 1,200 mEq diet. Four blacks and 4 whites were studied on 800 and 1,500 mEq sodium diets. To enable intake of 1,200 and 1,500 mEq sodium intravenous saline infusion was used. Blood pressure, sodium and potassium excretion, plasma renin activity and plasma aldosterone were measured at the end of each diet. Systolic blood pressure increased from the 10 mEq sodium diet to the 600 and 800 mEq sodium diet in blacks but not in whites. The systolic blood pressure increase was significant in both blacks and whites on the 1,200 and 1,500 mEq sodium diet when compared with blood pressure on the 10 mEq diet. Diastolic pressure significantly increased from the 10 mEq sodium to the 800 mEq sodium diet in blacks but not in whites. Plasma renin activity and plasma aldosterone concentration both decreased to similar extents with increase in sodium diet from 10 mEq sodium to 1,500 mEq sodium in both races. These researchers concluded that blacks are

more sensitive to the pressor effects of sodium than whites.

Three blacks and 3 whites were restudied on all the diets while they were maintained in zero potassium balance. The zero potassium balance was achieved by replacing the potassium excreed in previous day 24 hours by oral administration of potassium tablets. Maintaining a zero potassium balance attenuated the pressure increase due to sodium loading. The protective effect of potassium against the pressor effects of sodium load was confirmed. The authors suggested that this increased sensitivity to salt may contribute to the higher prevalence of hypertension in American blacks than in whites. This ties in quite well with the available epidemilogical data. However, the small number of subjects in this study and the unknown degree of genetic heterogeneity of the blacks make generalization of this finding of increased salt sensitivity to all blacks questionable.

American Blacks and whites consume similar amounts of sodium but blacks eat less potassium (Grim et al., 1980). The lower dietary potassium in blacks may be part of the cause of the higher prevalence of hypertension in that group. Less potassium implies less protection against the pressor effect of sodium load. The reduced sodium sensitivity in the presence of potassium was not explained by plasma renin activity or plasma aldosterone concentration because there was no racial difference in these hormone profiles.

The same investigators (Grim et al., 1980) had earlier shown that blacks exhibit delayed natriuresis in response to intravenous saline infusion compared to whites. This reduced rate of sodium excretion is independent of blood pressure and may represent impaired renal function. Rikimaru et al. (1988) examined the pressor response to sodium in the

natives of Papua, New Guinea in order to see whether the salt sensitivity was present in them as well as in American blacks. Normotensive men received a low sodium diet for three days. This was followed by a high sodium diet for another 10 days. Blood pressure, 24 hour sodium and potassium excretion, plasma renin activity and aldosterone concentration were measured at the end of each diet. Blood pressure significantly increased when the subjects wen from the low sodium to the high sodium diet.

Plasma aldosterone and renin activity both decreased as expected with increase in dietary sodium. The decreases in aldosterone and renin activity rules out a possible role for these two hormones in precipitating the blood pressure rise that was produced by the high salt diet. Kirkendall et al. (1975) studied normotensive American whites on a diet that provided 410 mEq sodium/day for 4 weeks. Blood pressure and total peripheral resistance did not change for the entire period of study. Burstzyn et al. (1980) trebled the sodium intake of British whites for two weeks. Blood pressure did not change in these subjects during the study. These studies demonstrate that whites as a race appear to be resistant to the pressor effects of sodium. Blacks as a race are sensitive to the pressor effects of sodium.

The phenomenon of sodium sensitivity was clearly shown in some normotensive humans in much the same way as Dahl et al. (1962) did in sensitive rats. It was still imperative to identify the same phenomenon in essential hypertensives if the salt sensitivity concept bore relevance to the subject matter of human essential hypertension.

Kawasaki et al. (1977) studied sodium sensiivity in 19 essential hypertensive patients. Antihypertensive medication was stopped for a

month prior to the study. The patients received a sequence of three diets providing 10 mEq, 100 mEq and 250 mEq sodium/day each for 7 days. Potassium intake was kept constant at 70 mEq/day for 21 days. Subjects were called sodium sensitive if their blood pressure increased more than 10% when they went from the 10 mEq to the 250 mEq sodium diet. Those subjects who either decreased their pressure or increased by less than less than 10% were considered sodium resistant. The sodium sensitive subjects retained more sodium and gained more weight. These results were duplicated by Fujita et al. (1980). These latter researchers used the same protocol on 18 essential hypertensives. With a high sodium diet, sodium sensitive subjects gained more weight, retained more sodium as found by Kawasaki et al. In addition, sodium sensitive subjects had a greater increase in cardiac output and increased plasma norepinephrine. The sodium sensitive subjects displayed lesser decrements in plasma renin activity, and plasma aldosterone concentation on the 250 mEq sodium diet when compared with sodium resistant subjects. The concentration of prostaglandin E2, a vasodilator and natriuretic agent, did not change in the sodium sensitive whereas it increased in the sodium resistant subjects on the 250 mEq sodium diet. These results together suggest that the greater increase in blood pressure in sodium sensitive patients on the 250 mEq sodium diet can be attributed to greater sodium retention and in turn to an increased cardiac output. The persistence of sympathetic nervous system activity in sodium sensitive subjects may contribute to the relative sodium retention with sodium loads and the observed increase in blood pressure.

The dietary intervention studies in both normotensives and essential hypertensives support the role of sodium in the development of

hypertension in sensitive individuals. Identification of subjects who are sodium sensitive warrants further investigation. It is the sodium sensitive subjects who can benefit from dietary sodium resriction. The diversity of blood pressure response to sodium argues against the global restriction of sodium in commercially avilable food.

The available literature indicates that in general, blacks are more sensitive to sodium than whites. In addition elderly subjects have been shown to be more sensitive than younger subjects (Zemel and Sowers, 1987).

Genetic Studies in Humans

American blacks have higher blood pressure than whites. This does not appear to be due to higher salt intake or body weight. The Evans County, Georgia data indicates that it could relate to more life stresses or to lower potassium intake. It could also relate to a genetic superiority in the ability of blacks to conserve salt, a disadvantage in our current day environment and society. A number of studies in whites suggest that blood pressure is determined primarily by genetic factors. For example, blood pressure tends to aggregate in families such that many members have low blood pressure or vice versa. Things that run in families can be nutritional cultural or genetic (Grim, 1987).

There is evidence that after birth environmental factors may not play a major role in the distribution of blood pressure in the white population. Adopted children at birth do not develop blood pressure patterns of the family they are adopted into (Zinner et al, 1971). No

similar data is available for blacks. Familial aggregation of blood pressure in blacks could relate to cultural, nutritional or environmental factors. Examples would include inner city stress or diets containing high sodium or low potassium or low calcium among families. Like whites, the ability of blacks to excrete sodium might correlate with the level of activity of renin angiotensin aldosterone axis. Higher levels of activity would have have a reduced ability to excrete sodium.

ANP metabolism may be genetically determined (Grim, 1987). An inappropriate decrease or lack of increase in secretion of ANP in response to a sodium load in blacks may account for a decreased ability to excrete sodium.

One way to test for the influence of genetic and environmental factors is to compare monozygotic (MZ) twins and dizygotic (DZ) twins. MZ are genetically identical so that any difference between them is due to environmental factors. DZ twins share half their genes but also share the environment. The twin study method requires that two conditions be met in order to be applicaable. First, the mean value of the trait should not differ between DZ and MZ twins and second, the variance in the MZ twins should not differ significantly from that in the DZ twins. The twin model can thus be used to assess the relative contribution of genetic and environmental factors. The next step is to measure the difference between twin pairs. This difference is narrower for MZ than for DZ. Mean within pair difference of MZ and DZ twins are then tested. If the mean is different this provides good evidence that a particular trait is under genetic control because it varies less in MZ than in DZ twins. Using the twin model in whites, blood pressure has

been found to be 80% genetically determined and the environment contributes 20% to the development of blood pressure pattern. The twin model will help establish the nature of sodium sensitivity if done in susceptible individuals. No data is available to address this issue in blacks (Grim, 1987).

Genetic Markers for Sodium Sensitivity

Clear, easily determined genetic markers are necessary if we are to be able to to identify the subjects who would benefit from sodium restriction. Reduction in sodium intake with the objective of preventing or treating hypertension is only beneficial to sodium sensitive individuals. Luft et al. (1987) have shown that measurement of phenotypes of haptoglobin can help identify sensitive from resistant subjects. Both normotensive and hypertensive subjects were tested for sodium sensitivity. Subjects with haptoglobin 1-1 phenotype are more likely to be sodium sensitive than phenotypes 1-2 or 2-2. Subjects with phenotype 2-2 are more likely to be salt resistant. This contention was supported by a study in another population, in which adults with haptoglobin phenotype 1-1 had higher pressure than those with phenotype 2-2. These studies together independently confirm the relationship between haptoglobin phenotypes and salt sensitivity. Tedde et al., 1988 have demonstrated increased sodium pump activity in red cells incubated with insulin. Increased fasting insulin reported in salt sensitive subjects may explain the increased retention of sodium. This antinatriuretic hormone appears to be higher in salt sensitive subjects than salt resistant. Clearly a lot of work needs to be put into the

sorting out of this relationship to become practically useful for prevention and treatment of hypertension.

Grim and Cantor (1986) investigated whether sensitivity to the pressor effects of sodium is genetic or environmental. To address this pertinent issue, twin studies have been done, to date just in white twin pairs. Both monozygotic and dizygotic twin pairs were involved in this study. The difference between monozygotic twin pairs is due to environmental factors whereas the difference between dizygotic twin pairs is due to genetic factors. From studies of this nature, it has been possible to establish that blood pressure has dependence on genetic inheritence. Salt sensitivity has been shown to be genetically transimitted so that it runs in families.

Potassium and Hypertension

Epidemiological Evidence

One of the strongest pieces of evidence supporting the role of dietary sodium as a cause of hypertension is the blood pressure in low sodium/low blood pressure populations. However, these populations also have a high potassium intake. Thompson and McQuarrie (1935) observed the marked hypotensive effect of potassium in a diabetic child with hypertension. This and other early studies sparked on the interest in potassium as a hypotensive agent. Sosaki et al. (1959) reported two population groups in Northern Japan, with similar sodium excretions but different blood pressures. The population with the higher potassium excretion had lower blood pressure. The population with the higher potassium excretion was in a region producing lots of apples, which

like most fruits, are rich in potassium. Consumption of 8 apples/day (70 mEq/day potassium), in the subjects with low potassium intake caused lowering of pressure in these people so that the two groups were similar in pressures.

All surveys comparing American blacks and whites have shown a higher excretion of potassium in whites than blacks (Berenson, 1982). Watson and colleagues studied 491 blacks and 181 whites. The 24 hour sodium excretion (in mEq) was 112 in black men, 98 in white men, and the potassium excretion was 28 in black men and 36 in white men. The sodium/potassium ratios were 4.1 in blacks and 2.9 in whites. The lower levels of potassium have been suggested to be partly responsible for the higher blood pressures in blacks than whites.

Grim and colleagues (1980) in Evans County, Georgia, used dietary recall and 24 hour excretion to estimate sodium and potassium intake. Blacks had higher blood pressures than whites. Whites ate 186 mEq sodium/day and excreted 162 mEq which was more than blacks who ate 136 mEq and excreted 130 mEq sodium/day. The potassium intake and excretion were respectively, 54 mEq and 40 mmEq per day in whites which were higher than in blacks who ate and excreted respectively 23 and 24 mEq potassium/day. However, the sodium/potassium ratio was higher in blacks than in whites. The higher sodium/potassium ratio in blacks than in whites may have been responsible for the higher blood pressures in blacks than whites. This study was quite valuable because it showed that dietary recall and 24 hour excretion of electrolytes produce similar results. This similarity in results from diet recall and 24 hour urinary excretion suggests that either can be used as a reliable estimate of electrolyte intake.

Potassium intervention studies

High potassium intake has received considerable attention because of epidemiological and direct experimental evidence suggesting it might be antihypertensive (Campbell, 1978).

Potassium infusion into a dog renal artery causes prompt diuresis and natriuresis that is thought to be due to inhibition of sodium reabsorption in the proximal tubule although other sites have been proposed. The diuretic effect of potassium has been shown in normotensive and hypertensive humans (Brunner, 1970). A dose dependent natriuresis has been shown to occur in reponse to administration of potassium up to 300 mM/day for 4 days (Bauer, 1979). A high potassium intake increases plasma aldosterone by direct effect of potassium on the adrenal cortex. This could modify blood pressure either by influencing renal handling of sodium or potentially by a mineralocorticoid event unrelated to a renal mechanism (Tannen, 1983). Despite a potassium induced rise in aldosterone levels, various studies have shown that high potassium intakes are natriuretic (Young, 1976). The importance of this aldosterone increase may be to limit excessive loss of sodium. The natriuresis induced by high potassium could play a significant role in its hypertensive effects. Indeed both salt loaded rats and spontaneously hypertensive rats, whose blood pressure is reduced by a high potassium diet, have a diminished exchangeable sodium space (Meneeley, 1958). Iimura (1981) reported a decrease in body weight, total exchangeable sodium, extracellular fluid space and plasma volume in hypertensive patients treated with high potassium diet.

Potassium supplementation lowered the threshold for baroreceptor activity and increased the sensitivity of aortic arch receptors in

normotensive humans (Skrabal, 1980). This increased sensitivity in the baroreceptors could prevent marked acute changes in blood pressure and attenuate the tendency for high blood pressure to develop.

Direct measurement of sympathetic function in sbjects on high potassium diet has not been very conclusive. High potassium diet produced reduction in blood pressure and norepinephrine excretion in siblings whose parents are hypertensive (Holly, 1981). These researchers, however, observed increased norepinephrine excretion and no change in blood pressure in siblings whose parents were normotensive. High potassium administration to SHR and WKY caused increase in neuronal uptake of norepinephrine only in SHR. This suggests high potassium may act by different mechanisms in different pathophysiological forms of hypertension (Diertz, 1981).

Potassium exerts a direct vasodilatory effect on resistance vessels at plasma concentrations that might be found with a high potassium intake (Haddy, 1983). Potassium intraarterial infusion causes prompt vasodilation. The response is due to direct arteriolar smooth muscle relaxation by potassium. This vasodilator response is abolished by ouabain which implies that it works through sodium potassium pump.

The presence of ouabain like material in plasma of animals with hypertension may be responsible for the impaired vasodilatory response to potassium in these animals. That is, depression of the sodium potassium pump by the plama substance would counteract the stimulatory effect of K, reducing its vasodilator influence (Overbeck, 1975; Haddy, 1988).

Calcium and Magnesium and hypertension

Epidemiological Evidence

There is not as much evidence for a possible role of calcium or magnesium in the development of hypertension as there is for sodium. Probably the first epidemiological evidence was the inverse relationship between the level of hardness of water and cardiovascular mortality in U.S.A. (Schroeder, 1960). Howeever, this relationship remains controversial (Belizan, 1983). Calcium in hard water may be sufficient to keep dietary intake above the required threshold value of total intake that protects against hypertension (McCarron, 1983 and 1986). The mechanism by which calcium is involved in blood pressure regulation was indicated by studies in SHR by McCarron and colleagues. SHR have low plasma renin activity, low plasma levels of ionized calcium and a compensatory increase in parathyroid hormone as well as a low plasma renin activity. Correction of the calcium deficiency not only corrected the hormone profiles but also lowered the blood pressure. This suggests a direct link between calcium, renin activity and hypertension and the reversibilty of these by dietary calcium. Whether this applies in humans has not been studied.

Langford et al. (1987) observed that there is a progressive increase in the ratio of calcium to sodium in the diet of low, middle and upper socioeconomic groups respectively, and the ratio of dietary calcium to sodium is lower in urban than in rural residents. They also observed that poorer urban families tended to have higher blood pressures. There tends to be low calcium intake in blacks whether they are above or below the poverty line. Milk intolerance or lactase deficiency may

explain this to some extent. It is not clearly established whether dietary calcium intake is a critical determinant of blood pressure level. If it is, it helps to explain the black/white blood pressure differences but does not explain the social class differences in blacks, because there are relatively few effects of social class on calcium intake.

Differences have been shown between normotensives and hypertensives in both animal and human subjects in calcium handling. In a study of newly diagnosed and uncomplicated essential hypertensives, McCarron et al. (1982) found that both normotensives and these hypertensives had similar age, sex, creatine, albumin, and total plasma calcium. The significant differences were the higher blood pressure and lower ionized calcium in the hypertensives compared to the normotensives. Low ionized calcium has also been demonstrated in spontaneously hypertensive rats (SHR). It has further been shown that there is abnormal membrane binding of extracellular calcium by membranes of SHR. The lower ionized calcium is a stimulus for parathyroid hormone production. Some antihypertensive agents, thiazides are known to cause positive calcium balance and return ionized calcium to normal. This is indirect evidence for the possible role of calcium contribution to the pathogenesis of hypertension.

Resnick et al. (1986) have related blood pressure, calcium and renin activity in human essential hypertensives. Their study has further supported the role of hypocalcemia in hypertension and placed it in the already known framework of blood pressure regulation. These investigators classified hypertensives on the basis of renin activity. Three levels of renin activity have long been described and include low

renin, normal renin and high renin essential hypertension. Low renin essential hypertension is the most common form. In this study most low renin subjects had low ionized calcium, low calcitonin, and high parathyroid hormone. This was in contrast to the high renin hypertensives who had normal or high ionized calcium and low parathyroid hormone and high calcitonin. Treatment of low renin essential hypertensives with calcium normalised renin, lowered blood pressure, normalised ionized calcium and returned the hormones to normal levels. Calcium treatment had either no effect or actually increased blood pressure in the high renin or normal renin hypertensives. This study suggests that low renin hypertension may be caused by low ionized calcium and that it is a true condition of hypocalcemia that will respond to calcium supplementation. Zozaya et al. (1988) observed hypertensives with both low ionized calcium and low total calcium. Although low calcium is usually associated with low renin hypertension, Kageyama et al. (1987) found that calcium supplementation lowered the blood pressure of rats with two kidney one clip hypertension. The hypotensive effect was related to the suppression of renin activity. This effect of calcium on renin activity was confirmed by failure of inhibitors of converting enzyme and angiotensin to potentiate the hypotensive effect of calcium. The failure of calcium to produce a hypotensive effect in human hypertensives with high renin is difficult to explain in the light of this finding in rats with high renin hypertension.

Hypocalcemia has been involved in other specific types of hypertension. Lopez-Jaramillo et al. (in press) demonstrated an association between low ionized calcium and pregnancy induced

hypertension. Only 4% of a group of nulliparous women who received supplemental calcium developed hypertension compared to 28% who developed hypertension in a group that did not receive calcium supplementation.

Abnormal calcium metabolism may mediate the hypertensive effect of sodium load and also play a causal role in essential hypertension. Hypertensives have higher than normal intracellular sodium. Increased intracelllar sodium in vascular smooth muscle may cause increased contractile activity. Increased intracellular sodium may result in increased intracellular calcium secondary to decreased exchange of sodium for calcium out. Increased intracellular sodium could lead to increased intracellular calcium, vascular smooth muscle contraction, increased vascular resistance and increased blood pressure. Cooper et al. (1988) reported that intracellular sodium and calcium in lymphocytes were higher in black subjects than in white subjects. If this difference is also true for smooth muscle cells, there may be a direct causal link among sodium, calcium and blood pressure.

Oshima et al. (1988) also showed that sodium sensitivity may be mediated by increased intracellular calcium. Acute sodium loading of normotensives induced significant increases in blood pressure, intracellular calcium. The calcium channel blocker, nifedipine, had an antihypertensive effect. Calcium is also a second messenger for angiotensin II in the stimulation of aldosterone secretion and vasoconstriction. Angiotensin II causes an increase in cytosolic free calcium in cultured smooth muscle cells. Increased cytosolic calcium increases contraction of vascularsmooth muscle and could thereby increase blood pressure (Rasmussen, 1985).

Dietary Fat

Smith-Barbaro et al. (1983) proposed that blood pressure increases that were associated with increased salt intake could have been due to other dietary factors. Animals fed a high salt diet alone developed hypertension, but they did not develop hypertension when high salt diet was given together with polyunsaturated fatty acids (PUFA). These effects of dietary fat were not altered by salt intake and the mechanism of the hypotensive effects of PUFA was not determined.

Pekka and Puska (1983) studied 57 families in the home environment after 2 weeks of baseline measurements. The subjects were assigned to 3 different groups: high PUFA diet, reduction of sodium from 192 to 77 mEq sodium per day, and the control diet. Blood pressure significantly decreased in the high PUFA only. The reduction was more marked in hypertensive subjects in this study group. A relative increase in the production of vasodilator prostaglandins were proposed as a possible mechanism because prostaglandins are lipids.

High levels of saturated fatty acids are known to compete with PUFA during cellular metabolism. In western diets, the high content of saturated fatty acids may compete with PUFA and raise blood pressure by limiting the production of vasodilator prostaglandins (Bursztyn, 1986).

Hill et al. (1980) proposed anoher mechanism by which dietary lipids may affect blood pressure. They studied a group of black Americans who consumed a vegetarian diet for 3 weeks. The subjects had reduced testicular hormone production. Because testesterone stimulates aldosterone production it could mediate blood pressure increase through sodium retention. The sheme might be, low dietary fat, low testesterone production, low aldosterone secretion and low blood pressure. A

comparison was made with a group of black South Africans whose usual diet was essentially vegetarian. Testesterone has been shown to stimulate aldosterone production which could then mediate the blood pressure increase through sodium retention. These latter subjects were put on an American diet for 3 weeks and showed marked increases in testosterone excretion. Thus saturated fatty acids have been implicated in the development of hypertension but the mechanisms are not yet well worked out.

Dietary Fiber

Blood pressures of animals increased when they were fed a diet rich in saturated fatty acids (Bursztyn, 1978). The presence of extra dietary fiber in the form of cellulose abolished these pressure increases although adding fiber to a normal diet did not affect pressure.

Wright et al. (1979) studied 42 normotensive subjects who were on different dietary fiber intakes. Dietary counselling was used to increase the dietary fiber by 80% in those who were initially on a low fiber diet and to lower by 50% the fiber content of those who were initially on a high fiber diet. Reduction of dietary fiber was associated with increases of both systolic and diastolic pressure. increasing the fiber content of the diet was associated with decreased blood pressure.

Groups of black and white American males on vegetarian diets for 3 weeks showed increased 24 hour excretion of testosterone (Goldin, 1982), suggesting a hypotensive mechanism involving aldosterone as described for PUFA above. which may have lowered the blood pressure. Steroid

hormone has been implicated as a mechanism through which fiber might influence blood pressure but the evidence is still inconclusive.

Carbohydrate and Blood Pressure

In 1961 Lewis Dahl found that lood pressure increased in 60% of rats that were fed large amounts of salt. These diets contained 72% sucrose by weight whereas normal rat chow has 45% carbohydrate by weight. There was speculation about a possible role of sucrose at this point in the development of hypertension.

Hall and Hall (1964) were working with uninephrectomized rats and found that feeding saline and different sugar solutions caused increase in pressure with some but not all sugar solutions. They attributed the blood pressre increase to the salt and proposed that the sweetness of the sugars made the animals drink more fluid including more salt.

Ahrens postulated a more direct role of sucrose in the development of hypertension. In 1974, his group assessed the effects of increasing sucrose intake in steps up to 200g/day in 26 normotensive volunteers. The subjects exhibited an increase in diastolic pressure at the 200 g level only.

The natriuretic response to hydration was studied. Solutions containing 5g sugar/kg body weight were administered to 20 normotensive subjects after 12 hours of fasting. Sucrose, glucose, fructose and lactose were antinatriuretic but galactose was not. This retention of sodium if manifested over a long time could be responsible for an increase in blood pressure. Ahrens also showed that deprivation of sucrose in rats caused natriuresis.

Alcohol and Hypertension

Attention was first drawn to the relationship between hypertension and alcohol by Lian in 1915 when he described the high prevalence of hypertension in heavy drinkers. In Los Angeles Heart Study (Clark et al., 1967), mean blood pressures were much higher in heavy than light drinkers or non-drinkers. A survey in Zimbabwe of 252 men and 250 women in both urban and rural areas with varying alcohol intakes showed no relationship between pressure and alcohol intake (Bursztyn, 1986).

Acute hemodynamic effects of alcohol are complex and evidence on the various aspects is conflicting. The acute effect of alcohol on blood pressure include the action of ethanol on cardiac contractility, autonomic control of cardiac function, preload and afterload hence it is difficult to be certain about the specifics of any of these parameters (Mahesweran and Beevers, 1986). Increased blood levels and urinary excretion of catecholamines have been reported following acute alcohol ingestion but not following chronic alcohol ingestion (Arkwright et al., 1982). There is no solid experimental evidence to explain the increase in blood pressure associated with increased alcohol intake.

Obesity and Blood Pressure

Obesity has long been recognized as one of the risk factors for the development of hypertension (Chiang, 1969). Body mass index (BMI), defined as weight in kg/ height squared in meters squared has a relatively high correlation with the amount of body fat and little with height. BMI is the best index of obesity as proposed at the National

Institute of Health in USA (Burton et al., 1985). Obesity can be defined as an excess of 20% or more of BMI the normal for men is 26.4 and 25.8 for women. Obesity is positively correlated with blood pressure in cross sectional studies (Larson et al., 1981).

Longitudinal studies have shown that weight gain is associated with increase in blood pressure. Abdominal fat has been reported to have a worse prognosis compared to peripheral "woman-type" fat (Bjorn, 1985). Both increased caloric intake and sedentary lifestyle which are both characteristic of obesity, have been associated with increase sympathetic activity and this may be the link between hypertension and obesity (Young and Landsberg, 1982).

A direct effect of obesity on metabolism such as impaired glucose handling and hyperinsulinemia which has also been shown to cause sodium retention may play a role in the development of hypertension (Berglund et al., 1985). In contrast to lean hypertensives, obese hypertensives tend to have expanded plasma volumes. This may be due to increased sodium retention caused by hyperinsulinemia (Langford, 1980).

A diet survey in Zimbabwe involving rural and urban population groups in which anthropometric data were collected showed low levels of obesity in this population (Bursztyn, 1986).

Evidence for Humoral Mechanisms in Hypertension

Renin Angiotensin System

Hypertension is a spectrum of pathophysiologic conditions including high renin, low renin, vasoconstriction and volume dependent hypertension. The endocrinology and attendant physiological mechanisms

can be vastly different at the two extremes of the spectrum even though the level of hypertension can be equivalent. There are broad differences in endocrinological, pathophysiological and pharmacologic responses which translate at one pole into low renin, wet, high flow, volume expanded hypertension and at the other, high renin, dry, low flow, ischemic and vasoconstricted hypertension (Laragh, 1982).

Several groups of investigators (Grim, 1987) have reported lower renin levels in blacks than in whites, but explanations for the difference have not been forthcoming. Helmer (1964) was the first to report this difference. He observed that 52% of 153 blacks with essential hypertension had no detectable levels of plasma renin activity (PRA) while only 31% whites with essential hypertension had similar values. In 1968 Helmer and Judson reported that young normotensive blacks had lower renin values than young whites..

Berenson et al. (1979) reported lower ambulatory PRA in black children than in white children. This renin difference could not be attributed to differences in sodium intake. This difference in renin between races which was apparent in childhood may be genetic, a view supported by studies in normotensive first degree relatives of hypertensives and monozygotic and dizygotic twins (Grim, 1987).

Cohen et al. (1982) reported that PRA was significantly lower in South African blacks with mild and severe hypertension than in normotensive subjects subjects. Malignant hypertensives with advanced renal failure had higher PRA and aldosterone levels than normotensives in the same study. Leary and Asmal (1975) reported no difference in PRA between normotensives and essential hypertensives in the Zulus of South Africa. All the reported values in this study were in the normal range

for PRA values.

In 1974, Jones et al. measured PRA in admitted patients with complicated hypertension in Zimbabwe. PRA was reported to be increased in these patients probably because most of them had some degree of renal failure. Renal biopsies were not done in these patients.

Renin cleaves a decapeptide, Angiotensin I from circulating angiotensinogen which is synthesized in the liver. The 2 terminal amino acids are removed by a kininase, angiotensin converting enzyme (ACE) to prodce an octapeptide called angiotensin II (AII). Most of the ACE is produced in the lungs.

The importance of the renin angiotensin system (RAS) in the maintanance of vascular tone is widely recognized (Brock 1985). The principal effector peptide of this system , AII initiates a sequence of biochemical events in vascular smooth muscle cells that result in contraction and this leads to increased total peripheral resistance. In vascular smooth muscle, AII causes a rapid increase in intracellular calcium ion concentration from mobilization of intracellular stores of calcium and influx of calcium from extracellular sources (Brock, 1985).

The evidence linking aldosterone to hypertension is substantiated by several observations (Genest, 1983). Excessive production of aldosterone in humans caused by zona glomerulosa hyperplasia has been shown by Davis and associates (1979) to have many of the biochemical characteristics of human essential hypertension. Increased urinary 3-oxo aldosterone conjugate has been found in mildly hypertensive patients with low, normal and high renin compared with controls (Drayer, 1981), which suggests that aldosterone metabolism is increased and may play a significant role in hypertension irrespective of the renin

status. Alterations of aldosterone responsiveness have been found in hypertensive patients. Aldosterone is significantly more sensitive to the administration of AII, ACTH and potassium in patients with essential hypertension than normotensive subjects. Aldosterone is inappropriately high in older normotensive subjects and low renin hypertensives in relation to PRA.

Leutscher et al. (1972) reported that patients with essential hypertension on a high salt diet (300 mM of sodium/day) have a significantly less suppression of aldosterone secretion, aldosterone excretion and plasma levels of aldosterone when compared to normotensive controls, whether the PRA was low, normal or high.

Atrial Natriuretic Peptide (ANP) and Hypertension

The heart functions as an endocrine organ which synthesizes, stores and secretes a peptide hormone into the circulation in response to atrial stretch (Debold 1985). ANP appears to influence circulatory homeostasis through its direct and indirect vasoactive and natriuretic actions (Villarreal et al., 1987).

Increased levels of ANP have been reported in patients with essential hypertension and several animal models of hypertension. Thus ANP secretion seems to be stimulated in hypertension irrespective of the specific pathophysiological mechanism responsible for the elevation of arterial pressure (Garcia, 1987). This is probably a result of increased left ventricular afterload, increased end diastolic volume and atrial stretch, a feature common to all hypertension.

The renal effects of ANP include natriuresis and increase in GFR. The increase in GFR appears to be a result of afferent arteriolar dilatation and efferent arteriolar constriction which are mediated by cyclic Guanosine Monophosphate (Humphreys and Lin, 1988). This hormone is known to counteract the effects of vasoconstrictors like AII and catecholamines (Laragh, 1984).

Although a role for ANP in normal body fluid physiology and in pathophysiological states has been sought with great intensity, there is no unanimity on the importance of this peptide in cardiovascular and fluid homeostasis.

Inappropriately high levels of PRA, arginine vasopressin (AVP), aldosterone (ALDO), and catecholamines (NE) have been observed in various subjects with essential hypertension (Cowley, 1986). To examine the ability of these various neurohormonal agents to modify each others chronic actions, modest elevations (in physiological range) of several of these hormones were intravenously infused by Cowley into normotensive chronically instrumented dogs. Aldosterone infusion alone into dogs for 11 days caused blood pressure to increase by 15 mmHg. Combined infusion of ALDO, AII, NE and AVp increased pressure by 15 mmHg as well. This study suggests that humoral synergism does not appear to play a major role in the development of chronic hypertension.

Summary

A lot of research has been done to find the mechanism of essential hypertension in American blacks who have a much higher prevalence of this disease than whites. A number of differences directly or

indirectly related to blood pressure and hypertension are recognized between American blacks and whites. Some of these differences include increased stress, low socioeconomic state, increased sensitivity to the pressor effects of sodium, and deficient dietary potassium among blacks. The multiplicity of factors involved and the heterogeneity of the problem makes it unlikely that a single factor is responsible for the difference between blacks and whites.

Urbanization has been associated with increase in the prevalence of hypertension in previously unwesternized population groups. Three explanations, increased dietary sodium, increased dietary sodium relative to potassium and increased psychological stress have been proposed as an explanation for this phenomenon. However, at present there is no convincing explanation for the effect of urbanization on blood pressure.

In our first study we investigated the pressor response to dietary sodium in young Zimbabwean men. Our working hypothesis for this study was Zimbabwean men are as sensitive to the pressor effects of sodium as are American blacks. In addition we predicted that this sodium pressor response would be attenuated by supplemental dietary potassium.

In our second study, we hypothesized that urban men are more sensitive to the pressor effects of dietary sodium than rural men. We also wanted to ascertain whether the predicted pressor sensitivity is modulated by potassium supplementation and mediated by failure to suppresss renin angiotensin aldosterone axis or failure of ANP to increase in response to a sodium load.

METHODS AND MATERIALS

Introduction

Blood pressure was examined in three population groups, each of which was studied on three different diets. The groups included 19 first year medical students, 20 low income men, and 20 low income urban men. Measurements were done while the men were eating a control diet which allowed them free access to salt; after 4 days on a low salt diet; and after 4 days on a high salt diet. The low salt diet provided 10 mEq sodium per day and the high salt diet provided 800 mEq of sodium per day. While on the high salt diet half of each group received 100 mEq of potassium (high potassium) per day and the other half did not get additional potassium (low potassium). The measurements taken included blood pressure, 24 hour urinary excretion of electrolytes and plasma concentrations of electrolytes, aldosterone, angiotensin II, and atrial natriuretic peptide. Women were excluded from this study except in the initial survey of medical students, because the menstrual cycle and medication for contraception are both known to influence blood pressure (Fisch and Frank, 1977). This was done to limit the number of variables in this already complex problem.

Medical Students

The first year medical students were selected as an initial group for study because they were accessible. Seventy one students, both males and females, were surveyed. Blood pressure was measured with subjects seated and 24 hour urine samples were collected from all of these students. From this group 20 normotensive male volunteers were selected, one of whom dropped out shortly before the study began. These subjects were selected because they had successfully completed a 24 hour urine collection and were normotensive during the screening period. Each signed an informed consent form. A financial incentive was offered for those who successfully completed the second part of the study. Of the 71 students who were screened, none was on medication for hypertension and two had blood pressures greater than 140/90 mmHg.

Rural Population

Selection Process

The rural population was selected after an informal survey of 1,000 residents in Chidamoyo revealed a low prevalence of hypertension. Dr. Cobb and Sr. McCarthy, the doctor and nurse respectively, at Chidamoyo mission hospital introduced us to the local chief, Chief Dandawa. The chief gave us permission to go ahead and do the research. We in turn contacted the local ruling majority party leaders and the village health worker in the region to enable good coordination during the research. All parties involved were enthusiastic to participate and rendezvous sites were easily selected. All people 15 years and older were asked to

come to these meeting sites. People in the vicinity of the rendezvous sites would gather at these places. These venues were not new, because the chief and the party officials frequently use them for meetings.

Altogether the blood pressures of 1,000 people were measured in three days by trained final year medical students. Calibrated mercury sphygmomanometers were used with standard adult cuff sizes. After the cuffs were inflated to levels above pulse obliteration pressure, the mercury column was allowed to fall at less than 2 mmHg/second. Readings were taken in duplicate 5 minutes apart. During the interval, a questionaire involving the background information on the subject was completed. The appearance of the first sound and the disappearance of the fifth sound were used as systolic and diastolic pressure respectively. The prevalence of hypertension defined as the percentage of subjects with blood pressure greater than 160/95 mmHg, was 7% in this survey. From this group, volunteeer male subjects who were willing to participate in the diet intervention study submitted their names. The research protocol was explained in detail and subjects were told that they would stay away from their families for two weeks. They were instructed not to eat any other food except that provided during the two weeks of study. The first 20 volunteers who were healthy men aged 20 years and older, who submitted their names were chosen to participate in the study. On repeat blood pressure measurement, one subject had a pressure greater than 140/90 mmHg. He was dropped from the study and a normotensive subject substituted for him. Written consent was obtained by having the subjects sign an "X" after their names after the consent was read to them. It was read to the men who agreed to to participate in the vernacular, Shona. A financial incentive was offered for those

who successfully completed the study. The volunteers were told that we had easy ways to tell if anyone drank alcohol or did not complete the 24 hour urine collection during the study. And they were told that if either or both were the case, no money would be given to the offender after the study.

Rural Location

Chidamoyo has a population of about 1000. It is about 200 miles from Harare, Zimbabwe's biggest city, and about 60 miles by gravel road from the nearest town, Karoi, which has a population of about 10,000. The gravel road to Karoi is an all weather road but in the rainy season it is unsafe and almost unusable by two wheel drive cars. On alternate days there is a morning bus from Chidamoyo to Karoi and beyond, usually to Harare. The bus reaches Karoi in the afternoon and does not return until the following morning, so that passengers have to stay overnight in Karoi. Consequently, people from Chidamoyo rarely go to Karoi.

Rural Population Characteristics

This population was classified as rural on the basis of a number of factors. The Chidamoyo area is a long distance from westernized population centers and poor transportation to and from these centers limits their influence. Day to day style of life, source of income and religious beliefs in Chidamoyo are little influenced by western culture (Gelfand, 1973).

This Chidamoyo area is inhabited primarily by the MaKorekore tribe. The MaKorekore culture is similar to most traditional cultures in this area of Africa (Gelfand, 1962). Most of the adults are illiterate,

although most of their children attend school. People in this area have almost no money and little major livestock (cattle, sheep, and goats). They rely mainly on subsistence farming. The farming equipment is simple and is comprised of hoes (for most people) or ox driven ploughs for tilling the land. The rains are a primary determinant of their income (Gelfand, 1971). Heavy rains would translate into good harvests and good income. In a good year the the annual family income is approximately $200 (US) with very little buying power.

The average family's fields average four acres and on which are planted corn, a variety of sorghum, millet, and beans. The dietary staples are "sadza," corn meal boiled into a thick porridge, and vegetables. The main protein source is beans, with irregular additions of goat, chicken and wild game meat and insects. The few major livestock are kept for reasons of prestige and so these animals are rarely killed for meat (Gelfand, 1971). Although a few people in this area have acquired large fields and have started to grow commercial crops like cotton and tobacco, these these individuals were not chosen as a participate in our study.

Most of the farming work is done in the summer months: November to April. Our study was done during the post harvest period: May to October. During this period, most men spend their days lounging around, attending public meetings, visiting relatives, doing the odd jobs at home or occasionally drinking traditional beer.

Most residents of Chidamoyo practise traditional religion. There are converts to the western religion spread from the mission church at Chidamoyo, however, the converts are mostly young women and they are a distinct minority. The people pray for a reason as do all people. For

example if rain is delayed, the community elders and the chief would present a "petition" to their ancestral spirits. Special traditional opaque beer is brewed and presented as a sacrifice. Rains eventually come after these deliberations, thus their prayers are answered.

Health care in this population is still traditional. Although the hospital where we did our research has been in existence for at least 25 years, western medical care is still a distant second choice to traditional medical care. Members of this population still prefer to attend traditional healers. Traditional healers not only treat the illnesses but they go a step further by telling the ill, who it was that caused the illness. This gives these patients a sense of relief as they can plan "revenge" on or to avoid the individual who made them ill.

If the traditional healers, "n'angas," fail to adequately treat anailment, patients do go to the hospital but they are frequently in advanced or terminal stages of disease. Because many of these patients die in the hospital, the credibility of western medicine.

Urban Population

Selection

The urban population was represented by a group of general workers at Parirenyatwa Teaching Hospital (PTH). These are low income ($200 US/month) men who had lived in Harare for at least three years. This group of workers participated in an International study, Intersalt (1986 and 1988) and so data on the prevalence of hypertension and intake of sodium and potassium in this population were available and reliable. The subjects were recruited by placing posters in their workplace.

Blood pressures of 24 volunteers were measured and hypertensives (n=3) were rejected. After informed written consent 20, (age matched to rural men) agreed to participate in the study. A financial incentive was offered for those who completed the study.

Urban Population Characteristics

Harare, the capital city of Zimbabwe, has a population of 800,000. The subjects of this study live in periurban townships five to ten miles from PTH. We classified this population as urban on the basis of a number of factors including access to a non-traditional diet, exposure to westernized ethnic, social, and moral values, crowded transportation and housing conditions, anxiety engendered by entering into a non-traditional society, and noise and atmospheric pollution (Gelfand, 1973; Murphree, 1969). Many races as well as African tribes are found in Harare. There is intermingling of these people and as a result, their culture is an admixture of several different racial and tribal influences.

The periurban housing is supplied with both water and electricity. People share small two to four room houses with as many as ten other individuals who represent as many as four different families. The high density of the housing precludes the use of land to grow vegetables or keep livestock.

These hospital workers have a strict daily 8 hour work schedule which starts at 7.00 a.m. except during weekends: Saturdays and Sundays. To be able to begin work at 7.00 a.m. these people would wake up as early as 4.00 a.m. in order to avail themselves of public transportation to PTH. Their late afternoons are free and usually spent preparing for

the following day's work or drinking beer. Apart from the financial restrictions these subjects have access to any food, social event, merchandise and other aspects of western lifestyle available in Harare.

The staple food in the urban area is, as in the rural area, "sadza." However, the urban workers have access to more meat and salt. Both public and private transport are much more efficient in the urban than in the rural men. In the urban areas, people practice mostly western religions (Metuh, 1981). Western medical care is extensively available for people living in the urban area. Traditional healers are present in the urban area, but are not as influential as western medical services. In Harare, patients ussually go to the traditional healers after western medicine has failed to treat the ailment (Gelfand, 1967).

Dietary Manipulations

Food for all three groups of subjects was prepared in centralized facilities, a special dining area in Parirenyatwa Hospital for the medical students and the hospital workers and in a missionary church cooking facility for the farmers. Diets were planned with the consultation of the chief dietitians at PTH, Mrs. Mhembere and Ms. Schlenke. All food in the serving dishes was weighed before and after serving the subjects to determine how much was consumed. Sodium content of foods was calculated from standard tables for sodium content of Zimbabwean foods (Chitsiku, 1981) plus the amount added in preparation. Total sodium consumed by a group each day was then divided by the number in each group to obtain the average sodium intake per individual per day. Details of the diets of each group follow.

Medical Students

For the medical students, standard menu items from the University food service were used. Meals elsewhere were not allowed. On the control diet free access to salt was allowed. On the low salt diet no salt was added to food during preparation or at table. Breakfast consisted of eggs, bread, corn meal porridge, fruit drinks and tea or coffee. Lunch and dinner consisted mainly of chicken, rice, beef, without salt, vegetables, and potatoes. Additional bread and fruits were provided as evening snacks.

When the subjects were on high salt diet, breakfast consisted of the above foods with known amounts of salt added in preparation, plus salami, bacon, milk, and cheese. For dinner and lunch the foods were similar to the low salt diet but additional known amounts of salt were added to the food during preparation. In addition 8 g of sodium chloride was ingested in the form of tablets which were taken with meals and at bedtime. In addition, half the group received supplemental potassium, provided as potassium chloride taken with meals.

Rural and urban Population

The rural group was accommodated in a church. A professional male cook normally employed by the University of Zimbabwe, prepared all the meals. A local assistant was hired to help with dishes and the fire preparation. No other source of food was allowed. Most of the food was obtained from the surrounding villages. This included vegetables, tomatoes, corn meal and goat meat. On control diet, subjects were provided with vegetables and small amounts of meat. Bread and tea with milk and sugar were also served. On low salt diet, vegetables were

prepared with no salt and corn meal which has negligible sodium content, was served. For an evening snack, fruit drinks and fruits were provided ad libitum.

On the high salt diet, the food was similar to the low salt diet except that salt was added to the food during preparation. In addition, there was more meat, margarine, and bread. Sodium and potassium were given as tablets as with the medical students.

The urban group was served a diet similar to that of the rural men except that there was more meat.

Accommodation During Research Period

During the entire period of study both the medical students and low income urban men were accommodated in the university dormitories and were transported to and from the central hospital where food was prepared and served three times a day. The rural men stayed in a church at Chidamoyo Hospital for the entire period of study, thus their activities were restricted, and food was prepared and served there.

Protocol

Measurements were taken at three levels of sodium intake according to the timeline shown in Figure 1. On day 0, subjects were screened for hypertension a final time. On day 1, the subjects arrived at the place of accommodation and began the control diet breakfast. On the afternoon of day 1, control measurements of pulse rate and blood pressure were made. In addition, the subjects began a 24 hour urine collection. They were instructed to void their bladder and then to keep all the urine

produced in plastic bottles stored in a carrying bag. During the morning of day 2, a blood sample was taken from a medial cubital vein with the subject in a relaxed seated position. This sample was analyzed for aldosterone, ANP, angiotensin, potassium, sodium calcium and creatinine. The 24 hour urine collection was completed on the afternoon of day 2. The urine was analyzed for sodium, potassium and calcium.

Low salt diet was began with dinner on day 2. On the afternoon of the 4th day, pulse rate and blood pressure were measured as part of a routine clinical assessment of the subjects. Increasing the frequency of blood pressure measurement may have also reduced the tendency of blood pressure to fall with repeated measurements (Bursztyn et al., 1980).

Measurements of experimental measurement of blood pressure was done on the afternoon of day 5 at which point a 24 hour urine collection was started. Blood samples were collected on the morning of the morning of day 6, and then the subjects were returned to a control diet until the morning of day 9. The high salt diet was begun on the morning of day 9 and clinical measurements of pulse rate and blood pressure were made on day 11. On day 12, blood pressure and pulse rate were measured for record and a 24 hour urine collection was begun. On day 13, blood samples were drawn and the 24 hour urine samples completed.

Blood Pressure Measurement

We used the blood pressure measuring protocol which was used by the Intersalt study 1986 (Intersalt 1988). This involves using a Hawksley random zero sphygmomanometer manufactured by Hawksley and Sons, West Sussex, England. The subject is allowed to sit quitely in a comfortable

position for 5 minutes. An initial blood pressure recording is preceded by measurement of pulse for one minute. After a cuff is applied, the pulse obliteration pressure is recorded and used as a guide for how far to inflate the cuff when measuring the pressure. The random zero knob is turned thrice to displace an unknown amount of mercury from a reservoir into the main column of the manometer. The cuff is then inflated to 20 mmHg above the pulse obliteration pressure and very slowly allowed to deflate at less than 2 mmHg/second. The first sound heard is taken to be the systolic reading, and the disappearance of 5th sound of Korotkov is used as the diastolic reading. The cuff is then disconnected from the manometer and the random zero figure recorded and subtracted from the readings for systolic and diastolic pressures. This procedure is repeated 5 minutes later. The average of the two values is used for statistical analysis. If these two measurements are different by more than 10 mmHg a third value is recorded in a similar manner and the closest two are averaged.

Laboratory Methods

Sodium and Potassium

Blood was collected into chilled plastic syringes by venepuncture of the median cubital vein. Serum was separated by centrifugation of clotted blood at 1700g for 15 minutes. Serum was stored at -4°C until analyzed. Urine was collected into plastic bottles with boric acid as preservative. Volumes of urine were measured. Aliquots were sampled from the total urine volume after thorough mixing. The urine samples were stored frozen until further analysis. Urine and serum sodium and

potassium were measured by flame photometry. A Corning Flame photometer (model 435) was used for the measurements.

Calcium

The same urine and serum samples used for sodium and potassium were used for calcium analysis. Calcium was analyzed using a reagent kit manufactured by Ciba Corning which employs the method of Moorehead and Biggs (1974). This color change reaction involves calcium reacting with o-cresophthalein complexone to form a purple color which absorbs light at 550 nm. The purple color is due to the formed calcium cresophthalein complexone complex. The intensity of the color is proportional to the calcium concentration. 8-hydroxyquinoline present in the reagent prevents interference from magnesium. A Hitachi Spectrophotometer model 100-60 was used.

Creatinine

Serum and urine were collected as above and stored frozen until time of analysis. A Hitachi Spectrophotometer model 100-60 was used for this assay. We used a reagent kit from Ciba Corning for these measurements. The assay is based upon the methodology of Jaffe which utilizes the reaction of creatinine and picric acid. Creatinine and sodium picrate in an alkaline medium react to form creatinine picrate complex. The formation of this complex causes an increase in absorbance at 510 nm which is directly proportional to the amount of creatinine in the sample. This absorbance is a linear function of creatinine concentration up to 20 mg creatinine/ml. Urine samples were diluted 1:15 with distilled water to produce concentrations that were in the

linear range.

Creatinine excretion coefficient was obtained by dividing 24 hour urinary creatinine excretion in mg, by the body weight in kilograms. This coefficient was used to assess the completeness of a 24 hour urine collection.

Atrial Natriuretic Peptide (ANP)

Blood Withdrawal

Upon collection as described above, blood was immediately transferred to polypropylene tubes containing EDTA (1 mg/ml blood) and aprotinin (500 kallikrein inhibitory units/ml blood). Samples were immediately centrifuged at 4°C at 1700g for 15 minutes to obtain plasma. Plasma was stored at -70°C until time of analysis.

ANP Radioimmunoassay

A radioimmunoassay specific for alpha human atrial natriuretic peptide developed and purchased from Peninsula Laboratories was used. This kit is designed to measure human alpha ANP and its related peptides by a competitive radioimmunoassay. The assay is based upon the competition of Iodine-125 human ANP and alpha human ANP (either standard or unknown) for binding to the limited quantity of antibodies specific for human ANP in each reaction mixture. As the quantity of standard or unknown in the reaction increases, the amount of Iodine-125 alpha human ANP bound to the antibody decreases. By measuring the amount of Iodine-125 human alpha ANP bound as a function of the concentration of alpha ANP in the standard reaction mixtures, it is possible to construct

a standard curve from which the concentration of alpha human ANP can be determined. The bound Iodine-125 human alpha ANP to antibody was measured by a Packard Auto Gamma 800 gamma counter. The ANP assay procedure requires two overnight incubations. On the first day, 100 microliters (µl) of unknown or standard are mixed with 100 µl of rabbit alpha human ANP antiserum. For the total binding, 100 µl of buffer replace the standard or unknown. The nonspecific binding tube has 200 µl of buffer. The reaction mixture is incubated at 4°C overnight.

During the second day 100 µl of iodinated ANP is added to each tube of the assay. This mixture is again incubated overnight at 4°C. On the third day, 100 µl of normal rabbit serum and 100 µl of goat rabbit anti-IgG serum are sequentially added to each reaction mixture and subsequently incubated at room temperature for two hours. The volume in each reaction mixture at this time is 500 µl. 500 µl of buffer is added to each tube and the mixture centrifuged at 1700g for 20 minutes to precipitate the bound antigen ANP. The free ANP is separated by careful suction using a water pump and decanted leaving a pellet which will be gamma counted. The interassay and intraassay variations were 8% and 6.5% respectively.

Aldosterone

Blood Withdrawal and Radioimmunoassay

Blood was collected as for electrolytes above and serum removed and stored frozen until analysis. The Coat-A-Count Aldosterone procedure was used for the assay. The Coat-A-Count Aldosterone No Extraction kit was furnished from Diagnostic Products Corp. Coat-A-Count Aldosterone is a solid phase radioimmunoassay designed for quantitative measurement

of aldosterone levels in unextracted serum. This assay employs serum calibrators, Iodine-125 tracer and antibody coated tubes. Aldosterone in the sample competes with radiolabeled aldosterone for antibody sites during a 3 hour incubation period. This tube is then decanted of free aldosterone both labeled and unlabeled, leaving the bound aldosterone on the tube walls. Gamma counting of the bound labeled for one minute gave the counts from which a standard curve and concentration of samples were determined. The interassay and intraassay variationswere 5.1% and 7.1% respectively.

Angiotensin

Blood Withdrawal and Extraction

Blood was collected as for the other analyses above and immediately transferred into chilled polyproplyene tubes containing 1 mg EDTA/ml. Plasma was immediately separated by centrifuging the blood at 1700g at 4°C for 15 minutes. Three ml of chilled absolute ethanol was added to 1 ml of plasma and vortexed and centrifuged at 4°C for another 15 minutes. The supernatant was decanted and retained on ice. One ml of cold ethanol was added to the precipitate and vortexed and centrifuged as above and the supernatant decanted in the previously retained supernatant samples on ice. The precipitate is discarded. The total volume of approximately 4 ml of supernatant is dried down in a 40°C waterbath by blowing compressed air into the tubes above the supernatant overnight. The dried samples are immediately preserved frozen until further analysis by radioimmunoassay.

Angiotensin II radioimmunoassay

The radioimmunoassay for AII depends on the competition between cold AII either in the standard or in the unknown and Iodine-125 radiolabeled AII. There is 100% cross reactivity with angiotensin III.

The assay procedure involves one 24 hour incubation period. On the first day of the analysis, the dried down AII samples are reconstituted with 200 µl of buffer. Aliquots of 100 µl of standard or unknown AII are vortexed with 50 µl of radiolabeled AII containing about 10,000 counts/minute and 100 µl of AII antisera. The mixture is incubated for 24 hours at 4°C. Twenty four hours later the bound and unbound AII are separated using freshly prepared dextran activated .01% charcoal in buffer. One ml of charcoal is added to the incubated mixture and vortexed and centrifuged at 1700g for 10 minutes. The supernatant is immediately decanted and retained in labeled tubes and gamma counted for bound AII, whereas the charcoal precipitated free AII is discarded. A standard curve is constructed from the concentrations of the standard AII in the reaction mixtures and used for determining the concentrations of the unknown AII. The interassay and intraassay variations were 6.8% and 3.2% respectively.

Statistical Methods

Statistical comparisons between control salt, low salt and high salt diet values were made using mixed design analysis of variance (ANOVA) (Steel and Torie). Multiple comparisons were only made if the calculated F statistic from ANOVA was greater than the critical F statistic (n=20, alpha=0.05). Bonferroni's t statistics was used for within group and between group comparisons.

Students' t test was used to compare high sodium-high potassium and high sodium-low potassium groups.

All results are reported as MEAN $\pm$ SEM. Statistical significance between mean values were shown using a P value of 0.05.

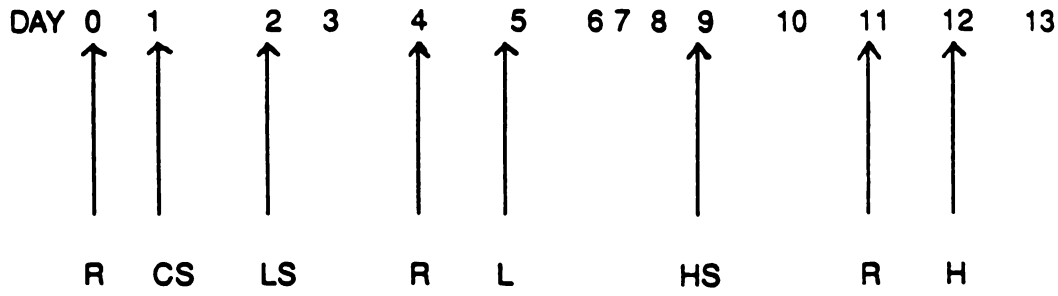
RESULTS

Introduction

Our studies can be divided into two groups: studies on medical students and studies on urban and rural workers. The medical students were studied first in order to determine the feasibilty of this type of work under the conditions of our experiments and to determine if young Zimbabwean males exhibited the same pressor response to sodium as did American blacks. Urban and rural males of an average age older than the medical students were studied next. They were studied to ascertain if there are differences in the response to dietary sodium in urban and rural individuals from populations with very different prevalences of hypertension. We also studied the influence of dietary potassium on the pressor and humoral responses to sodium.

Medical Students

Completeness of 24 hour urine collection was confirmed by creatinine excretion coefficients which were 29±2 mg/kg body weight/24 hours on the control diet and 37±2 mg/kg on the low salt diet and 30±1 mg/kg on the high salt diet. These values are all within the normal range of creatinine excretion coefficients (8-40 mg/24 hrs/kg body weight). No data were excluded from the study on the basis of incomplete urine



R = routine blood pressure measurement

CS = control salt measurements

LS = low salt commencement, L= low salt measurements

HS = high salt commencement, H = high salt measurements

Figure 1. Experimental protocol

collection.

Sodium

Table 2 shows 24 hour urinary sodium excretion on control diet value of 247±14 mEq, low salt diet value of 23±2 mEq and the high salt diet value of 684±81 mEq. Serum sodium concentration did not significantly change throughout the study.

Potassium

Potassium excretion was 63±3 mEq on the control diet 64±4 mEq on low salt diet in our subjects as shown in Table 2. Potassium excretion was respectively 169±3.9 mEq on the high sodium, high potassium diet and 93±9.7 mEq on high sodium and low potassium diet. Serum potassium did not significantly change in any group throughout the study.

The sodium/potassium ratio calculated from 24 hour urinary excretion of these cations was 0.4±0.05 on low salt diet and 3.3±0.16 and 6.8±0.5 respectively on high and low potassium subgroups of high salt diet. The control sodium/potassium ratio was 4±0.2.

Calcium

Calcium excretion was 4.3±0.7 mMol/24 hours on control diet and 4.7±0.7 mMol on high salt diet as shown in Table 2. The increase of calcium excretion from 1.6±0.3 mMol to 4.7±0.7 mMol/24 hours was significant as shown in Table 2. Total serum calcium concentration did not significantly change in any group throughout the study.

Body

Body weight was 65±2 kg on control diet and 64±2 kg on low salt

Parameter	Control diet	Low salt diet	Low-Hi Diff	LO-Hi+K Di
Sodium excretion mEq in 24 hrs.	247±14+	23±2*	-573±31	-545±25
Potassium excr. mEq in 24 hrs.	63±5+	64±3	-26±9#	-110±6
Calcium excretion mmol in 24hrs	4.3±0.7	1.6±.3*	-2.9±0.7	-3.3±1
Creatinine ex. coe in mg/kg/24 hrs.	29±2	37±2*	+9±2	+2.5±0.2
Sodium/potassium ratio	4±0.2+	0.4±0.05*	-6.4±0.5	-3±0.1
Plasma Calcium mmol/l	2.5±.07	2.4±.09	+0.1±0.07	+0.1±0.1
Body weight in kg	65±2	64±2*	-3.1±0.3	-3.6±0.5

* = p<.05 low vs high salt

#=p<.05 high salt low K vs high K

+= p <.05 control vs high salt

LO-Hi +K Dif= Difference between low salt and high salt with potassium supplementation

Low- Hi Diff= difference between low salt and high salt

Table 2. Electrolytes and related variables on three sodium diets.

diet. Body weight significantly increased to 68±2 kg on high salt diet.

Cardiovascular Responses

Systolic blood pressure changes are shown in Fig. 2 and Table 3. Systolic blood pressure was 119±2 mmHg on control diet, 113±2 mmHg on low salt diet and 121±2 mmHg on high salt diet.

Diastolic pressure was 69±2 mmHg on control diet, 79±2 mmHg on low salt diet and 72±2 mmHg on high salt diet. Diastolic blood pressure significantly decreased from low salt to high salt diet.

Mean arterial pressure (MAP) was calculated as the sum of distolic pressre and a third of pulse pressure. MAP was 86±1 mmHg on control diet. MAP was 90±2 mmHg on low salt diet which was not significantly different from 88±1.5 mmHg on high salt diet.

Pulse pressure was calculated as the difference between systolic and diastolic pressure. Pulse pressure was 51±2 mmHg on control diet. The pulse pressure significantly increased from 34±1 mmHg on low salt diet to 49±2 mmHg on high salt diet.

Pulse rate was 74±2/minute on control. Pulse rate of 79±2, on low salt diet, was not significantly different from 77±2 on high salt diet.

Hormonal responses

Control plasma aldosterone was 133±15 pg/ml. Plasma aldosterone concentration decreased significantly from 505±41 pg/ml on low salt diet to 103±13 pg/ml on high salt diet.

Control plasma ANP concentration was 178±5 pg/ml. Low salt diet ANP was 165±5 pg/ml which was not significantly different from 158±6 pg/ml on high salt diet as shown in Fig. 3.

Parameter	Control diet	Low salt diet	Low to Hi Diff	Low to Hi+K Diff
Systolic pressure mm Hg	119±2 +	113±2 *#	-10.8±2	- 5.3±1.7
Diastolic pressure mm Hg	69±2	79±2 *#	5.7±1.6	7.3±2.8
Mean arterial pressure mm Hg	86±1	90±2 *	0.2±1.4	3±1.9
Pulse pressure mm Hg	51±2	34±1 *#	-16.5±2.5	-12.7±3.6
Pulse rate/min	74±2	79±2 *	3.4±2.7	0.4±2.5

*= p<.05 low vs high
+ = p<.05 control vs high
#=p<.05 control vs low
Low to Hi Diff=difference between low salt and high salt
Hi +K Diff= Difference between low salt and high salt plus potassium supplementation

Table 3. Cardiovascular responses to dietary sodium in young Zimbabwean men.

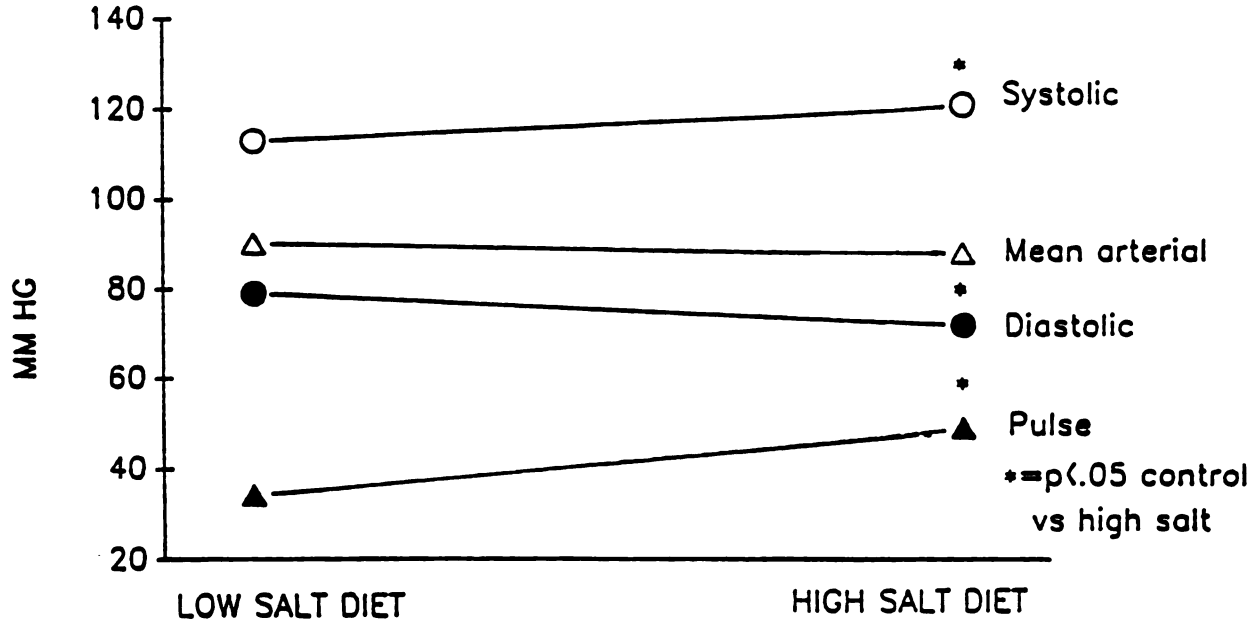


Figure 2. Blood pressure response to sodium in young Zimbabwean men.

Plasma AII significantly decreased from 25±3 pg/ml on low salt diet to 16±2 pg/ml on high salt diet as shown in Fig. 4. AII concentration was 28±4 pg/ml on control diet.

Potassium Supplementation

Potassium supplementation significantly increased kaliuresis as shown in Table 2. Cardiovascular responses were not significantly altered by potassium although there was a tendency for attenuation of the systolic blood pressure increase. Plasma AII was significantly higher with potassium supplementation while plasma aldosterone concentrations tended to increase with potassium supplementation but the change was not significant as shown in Table 4.

Urban and Rural Men

Electrolyte Excretion

Sodium

Table 5 shows the sodium excretion on low salt and high salt diets in both urban and rural men. The control 24 hour urinary sodium excretion was 142±10 and 130±15 mEq for urban men and rural men respectively (not significantly different). The creatinine excretion coefficients and low sodium excretions recorded shown in Table 5 demonstrate that good compliance was obtained in both groups.

The low salt diet sodium excretions rates were 25±4 mEq for urban men and 14±3 mEq for rural men. These excretion rates are consistent with sodium intake which is expected to be less than 30 mEq in subjects

Hormone	Control diet	Low salt diet	Low to Hi Na	Low to Hi Na +K
ANP pg/ml	178±5#	165±5	12.7±9	2±17
Aldosterone pg/ml	133±15	505±41*+	413±53	415±60
A II pg/ml	28±4#	25±3+	9±5	14±4

*=p <.05 control vs low

#= p <.05 control vs high

+=p <.05 low vs high

Low to Hi Na =low salt to high salt diet difference

Low to Hi +k =Low salt to high salt plus potassium difference

Table 4. Hormone response to dietary sodium in young Zimbabwean men.

PG / ML

550

450

350

250

150

50

Figure

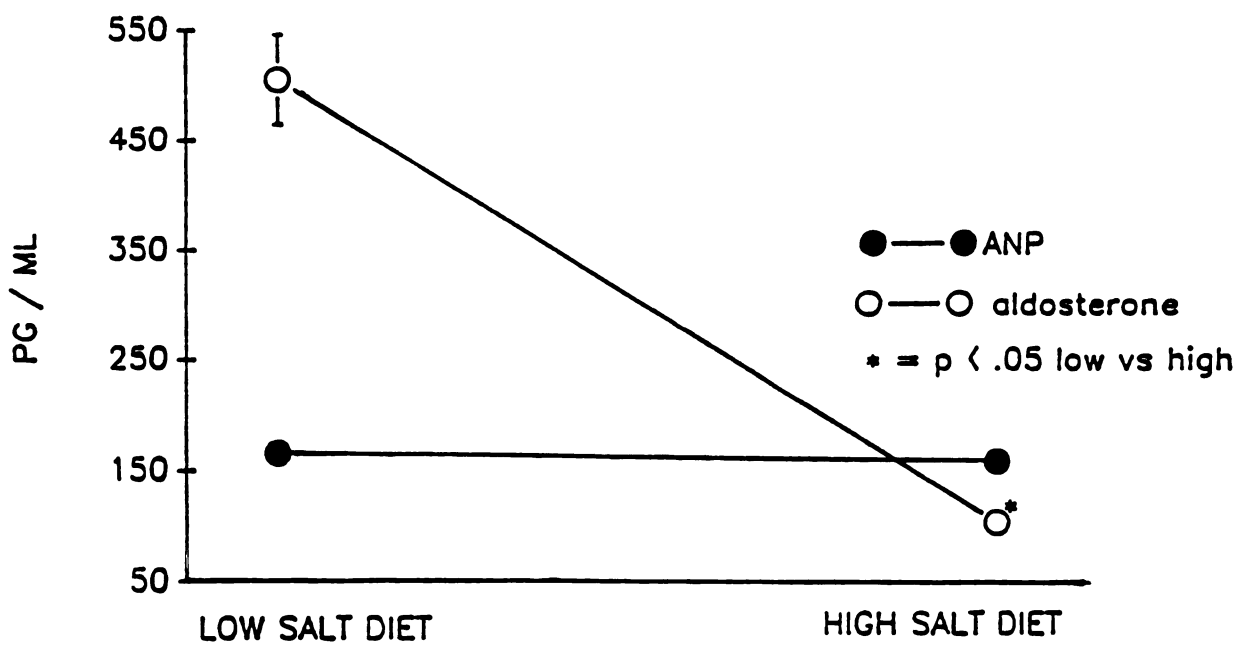


Figure 3. Plasma Aldosterone and ANP response to sodium in young men.

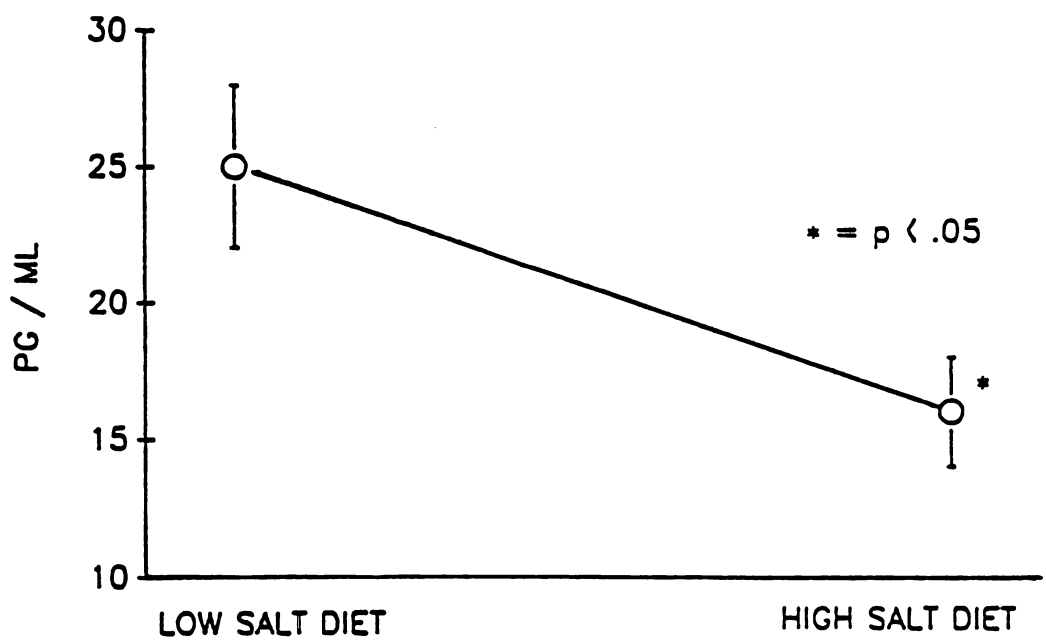


Figure 4. Angiotensin II response to dietary sodium in young Zimbabwean men

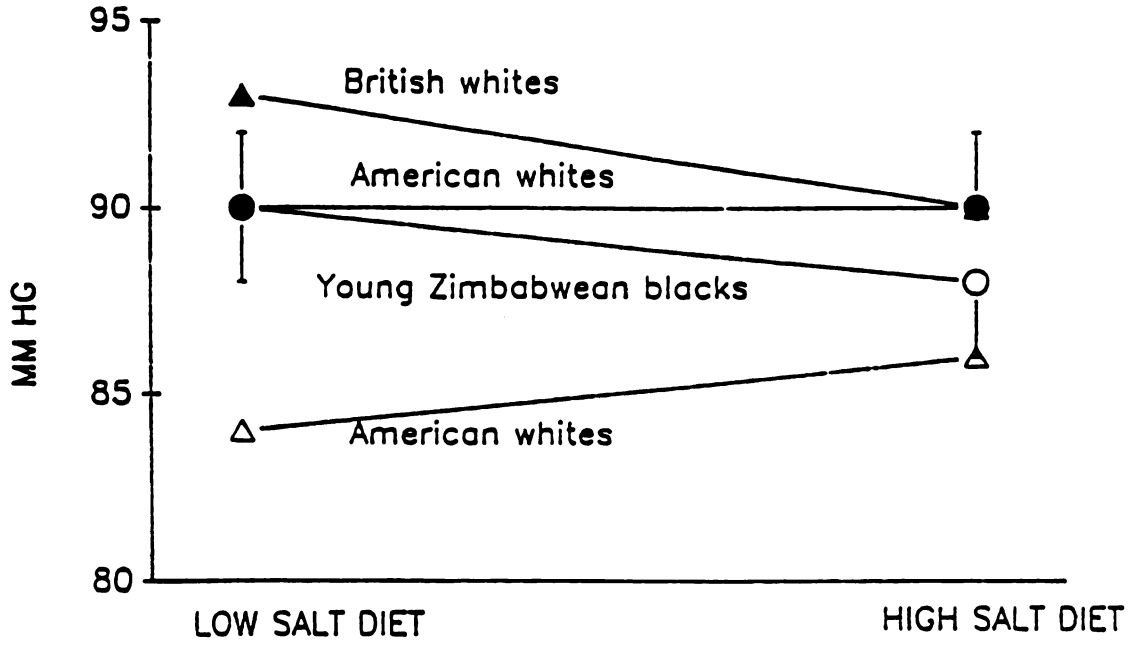


Figure 5. Mean arterial pressure on sodium load in black and white men

PARAMETER	CONTROL DIET	LOW SALT DIET	LOW TO HIGH DIFF. LOW K	HIGH K
Sodium Excretion in mEq/24 hrs	130±15 142±10	14±3 25±4	-411±54 -477±40	-366±21 -499±30
Potassium Excretion in mEq/24 hrs	43±3 38±3	34±4.5 55±9	-5±8# -21±18#	-37±3 -53±10
Calcium Excretion in mMol/24 hrs	1.3±.2 1.5±.2	0.7±.2*+ 1.6±.2+	-2.3±0.5 -2.3±0.5	-2±0.5 -2.8±0.6
Molar urinary sodium/ potassium ratio	3.05±.3 4±.3	0.4±0.1 .0.5±0.05	-2±1# -11±1#	-5.6±0.5 -5±0.5
Creatinine excretion coefficient mg/kg/24hrs	19.5±1.4 17±5	17±2 23±11	+3±1.4 +5±5	+6.3±.7 +6±5
Body weight in kilograms	54.7±1.4 62.5±2	55.2±1.5 63±1.9	-4±1 -4±0.5	-3.4±0.7 -4.5±0.1
Urine osmolarity in mosmols	401±37 604±13	202±20 435±13	-266±51 -63±13	-375±48 -40±12
Plasma aldosterone in pg/ml	146±39 96±9	161±29 326±46*+	+126±37# +284±56	+65±53 +191±79
Plasma ANP in pg/ml	184±9.5 182±7	128±10*+ 167±4.6	-59±18 -11±8	-49±24 -10±13

* = p< .05 control vs low salt diet values

+ = p <. 05 low salt vs high salt diet values

= p < .05 effect of potassium on high salt diet

upper rows =rural men
lower rows = urban men
DIFF. =Difference

Table 5. Electrolytes and related variables in urban and rural men.

who eat solely unprocessed food with no added salt (Rikimaru et al., 1988).

The high diet sodium excretion was 513±25 mEq for urban men and 402±29 mEq for rural men. The urban men excreted significantly more than rural men on both low salt and high salt diet as shown in Table 5.

Potassium

Table 5 shows that potassium excretion for the two groups was similar. The control potassium excretion was 38±3 mEq for urban men and 43±3 mEq for rural men. Both of these potassiunm excretion rates are lower than control excretion rates observed in the medical students who ate a typically western diet. On low salt diet, urban men excreted significantly more potassium than rural men on low salt diet. The urban men excreted 45±4 mEq potassium on high salt diet and 98±9 mEq on high sodium high potassium diet. The rural men excreted 34±4 mEq on high sodium diet and 65.7±5 mEq on high sodium high potassium.

Calcium

Control 24 hour urinary calcium excretion was 1.5±0.2 mMol in urban men and 1.3±0.2 mMol in rural men respectively. The low salt diet calcium excretion 1.6±0.2 mMol for urban men and 0.7+0.2 mMol in rural men as shown in Table 5. Both urban men and rural men exhibited significant calciuresis of 2.9±0.4 mMol and 4±1 mMol respectively.

The total serum calcium concentration did not significantly change in any group throughout the study.

Cardiovascular Responses

Control systolic blood pressure was 116±3 mmHg for urban men and 117±3 mmHg for rural men. Low salt diet systolic pressure was 109±4

PARAMETER (pressure in mm Hg)	CONTROL DIET	LOW SALT DIET	LOW TO HIGH DIFF. LOW K	HIGH K
Systolic pressure	117±3 116±3	107±2 *+ 109±2*+	-17±4 -15±5	-14±2 -19±5
Diastolic pressure	67±3 74±2	65±3 68±2	-7±6 -0.5±2	-1.3±3 -3.5±2
Mean arterial pressure	84±3 88±2	79±2+ 82±1*+	-10.8±5 -5±3	-5.4±2.5 -8.8±3
Pulse pressure	51±3 43±2	42±4*+ 41±3+	-11±5 -14±4	-12±3 -16±4
Heart rate/ minute	74±3 67±2	74±2 80±2*+	+11±3 +18±4	+2±4 +10±4

* =p <. 05 control vs low salt diet values

+ = p < . 05 low salt vs high salt diet values

upper row =rural men

lower row = urban men

DIFF =Difference

Table 6. Cardiovascular responses to dietary sodium and potassium.

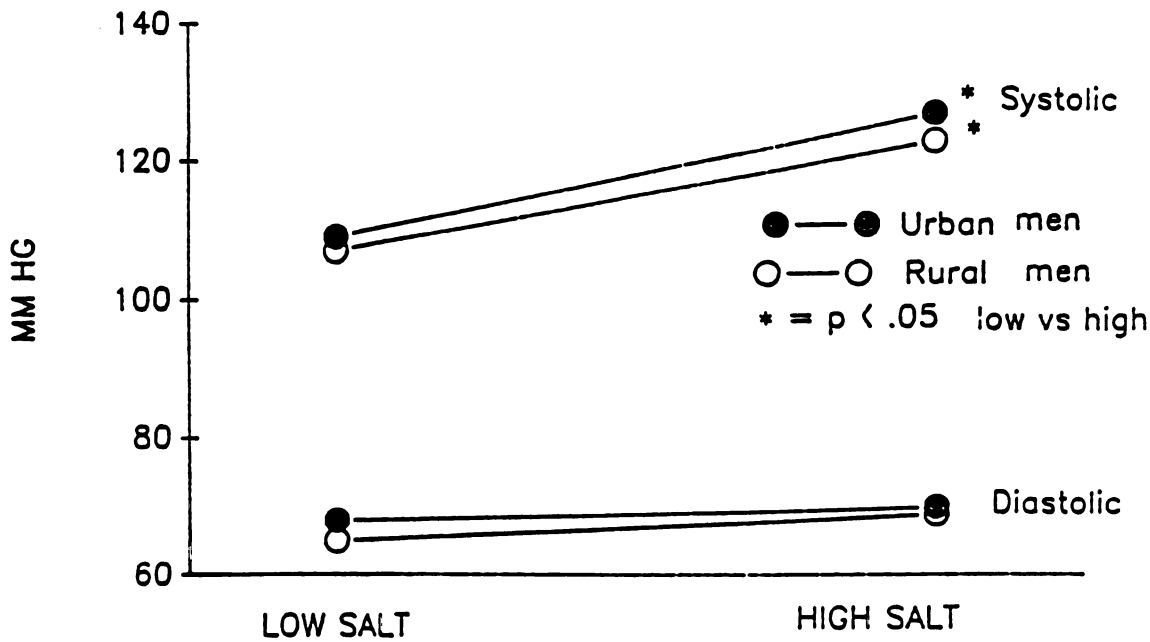


Figure 6. Blood pressure response to dietary sodium in urban and rural men

mmHg in urban men and 107±2 mmHg in rural men. The systolic blood pressure significantly increased to 127±4 mmHg in urban men and to 123±3 mmHg in rural men on high salt diet.

Diastolic pressure did not significantly change throughout the study as shown in Fig. 7 and Table 6.

Control MAP was 88±3 mmHg for urban men and 84±2 mmHg for rural men. Low salt MAP was 82+1 mmHg in urban men and 79+2 mmHg in rural men. MAP significantly increased from low salt to 89±2 mmHg in urban men and 87±2 mmHg in rural men on high salt diet as shown in Fig. 7 and Table 6. There was no significant difference between the two groups on each diet.

Pulse pressure values on control, low salt and high salt diet were repectively, 43±2, 41±3 and 56±3 mmHg for the urban men and 51±3, 42±3 and 54±2 mmHg for the rural men. On low salt diet, pulse pressure did not change in urban men but significantly decreased. The widening of pulse pressure due to volume expansion by sodium load was observed in both groups.

Heart rate did not significantly change in these men as shown in Table 6.

Hormonal Responses

Control plasma aldosterone concentration was 96±9 pg/ml in urban men and 140±30 pg/ml for the rural men. These values were not significantly different. There was a tendency for aldosterone to be lower in the urban men than in rural men. On low salt diet plasma aldosterone was 326±46 pg/ml in urban men which was significantly higher than 161±29 pg/ml in rural men. Plasma aldosterone concentration was significantly higher in urban men than rural men on low salt diet. High salt diet

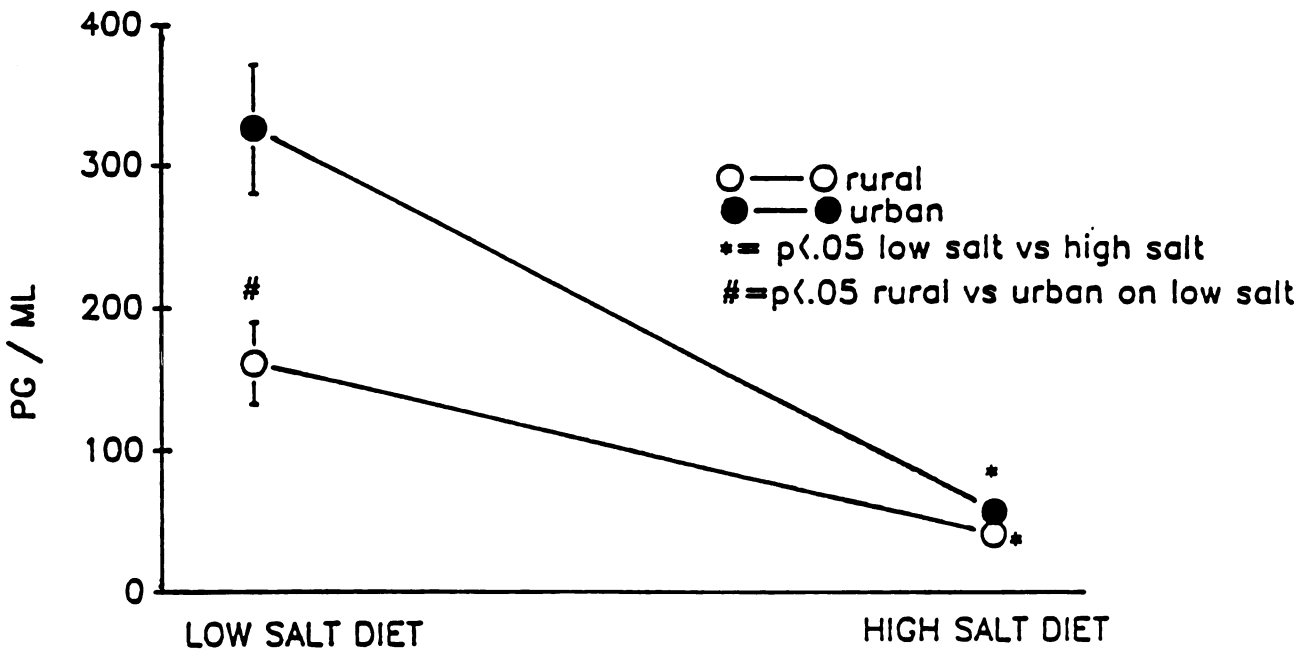


Figure 7. Aldosterone response to sodium in urban and rural men

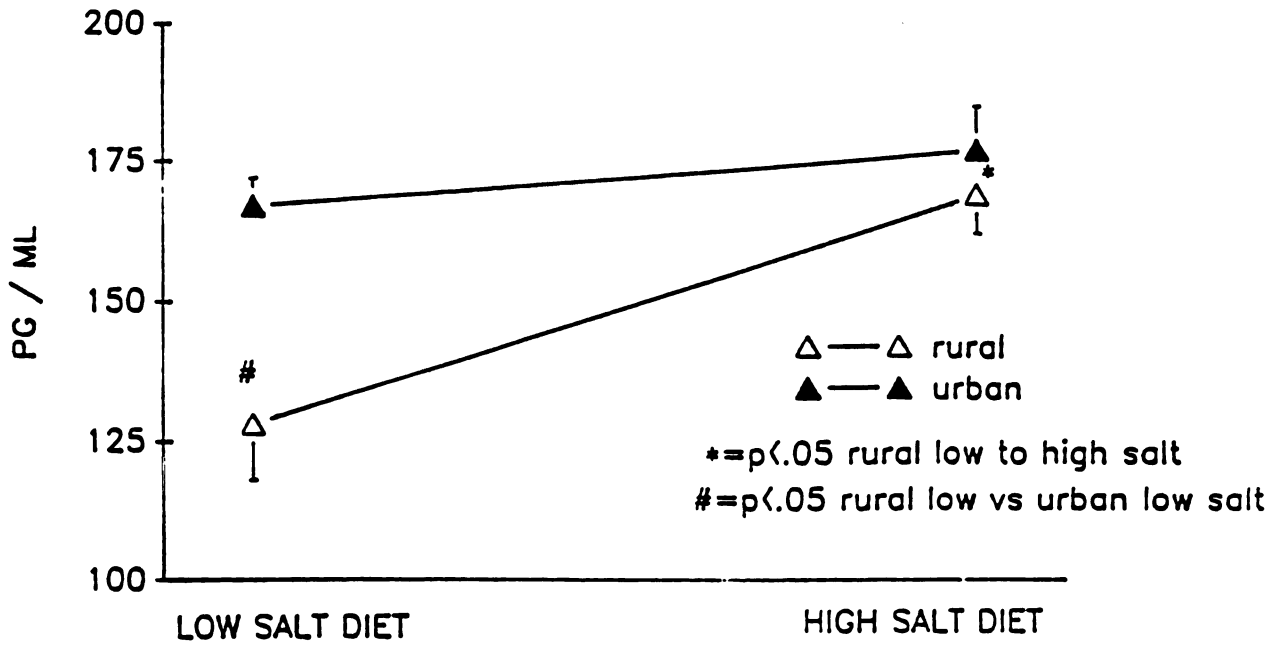


Figure 8. ANP response to dietary sodium in urban and rural men

Group	Age in years	Height in cm	BMI in kg/sq.m
Med students	19.4±.14	173±1.6	21.7±0.4
Rural men	39±2.7	172±1.8	18.4±0.3
Urban men	37±2.4	169±0.8	22.2±0.5

Table 1. Baseline parameters of all three groups of men.

significantly reduced plasma aldosterone concentration to 57±9 pg/ml in urban men and 41±9 pg/ml in rural men as seen in Fig. 11 and Table 7. Potassium supplementation significantly increased aldosterone concentration only in rural men as shown in Table 4.

Control plasma ANP was 169±9 pg/ml in urban men and 184±9 pg/ml for rural men. Low salt ANP was 167±5 pg/ml in urban men and 128±10 pg/ml in rural men. The high salt ANP was 177±8 pg/ml for the urban men and 182±7 pg/ml for rural men. There was a significant increase in ANP when subjects went from low salt to high salt only in rural men as shown in Fig. 9 and Table 5.

Potassium Supplementation

Potassium supplementation significantly attenuated the supression of aldosterone by high salt in rural but not in urban men, but did not significantly alter the cardiovascular or the other hormonal responses to sodium load as shown in Table 5.

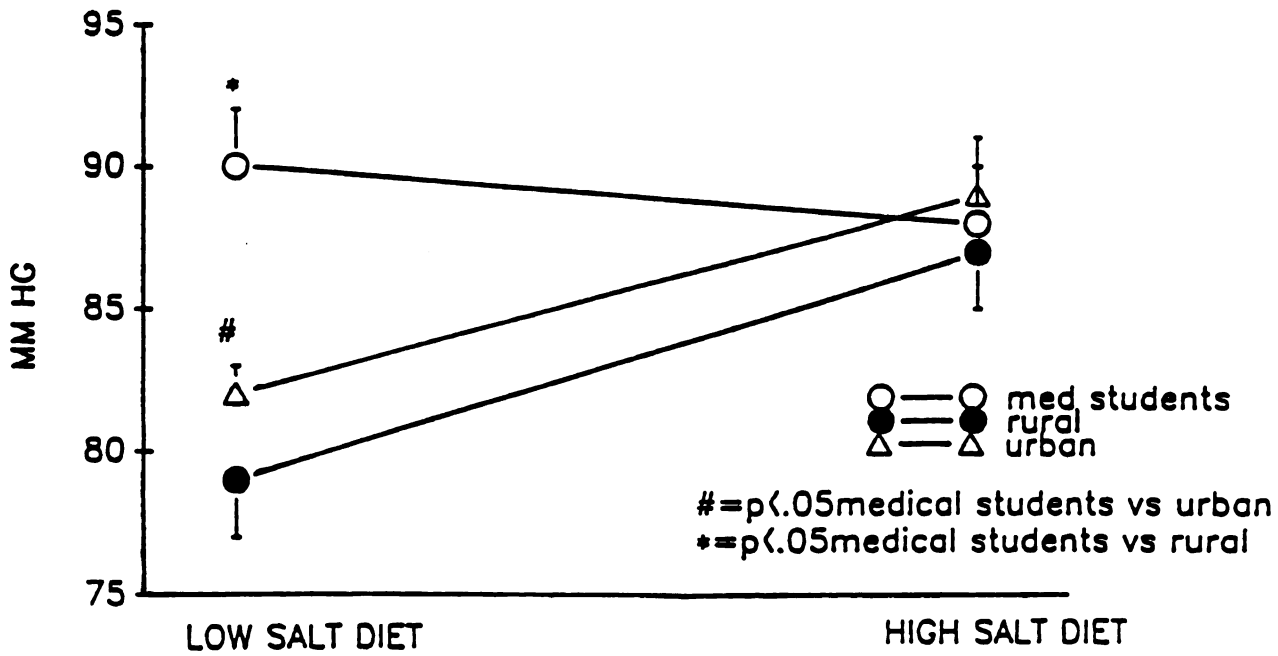


Figure 9. Mean arterial pressure response to sodium in black men.

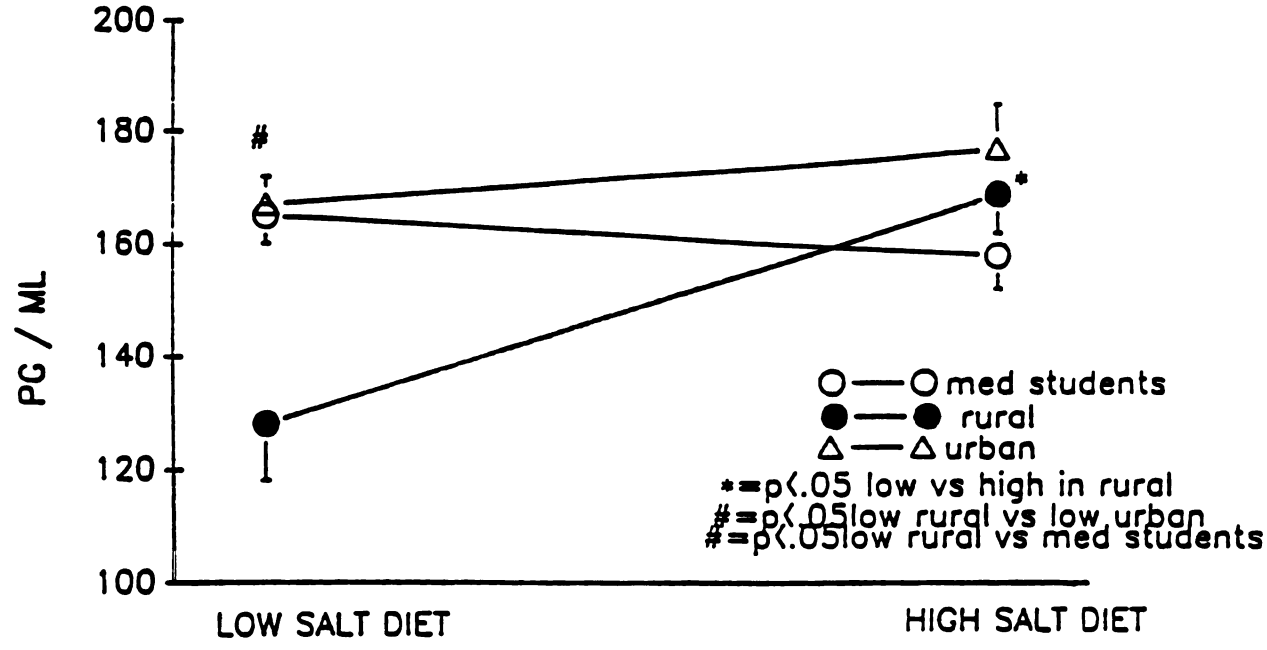


Figure 10. ANP response to dietary sodium in black men

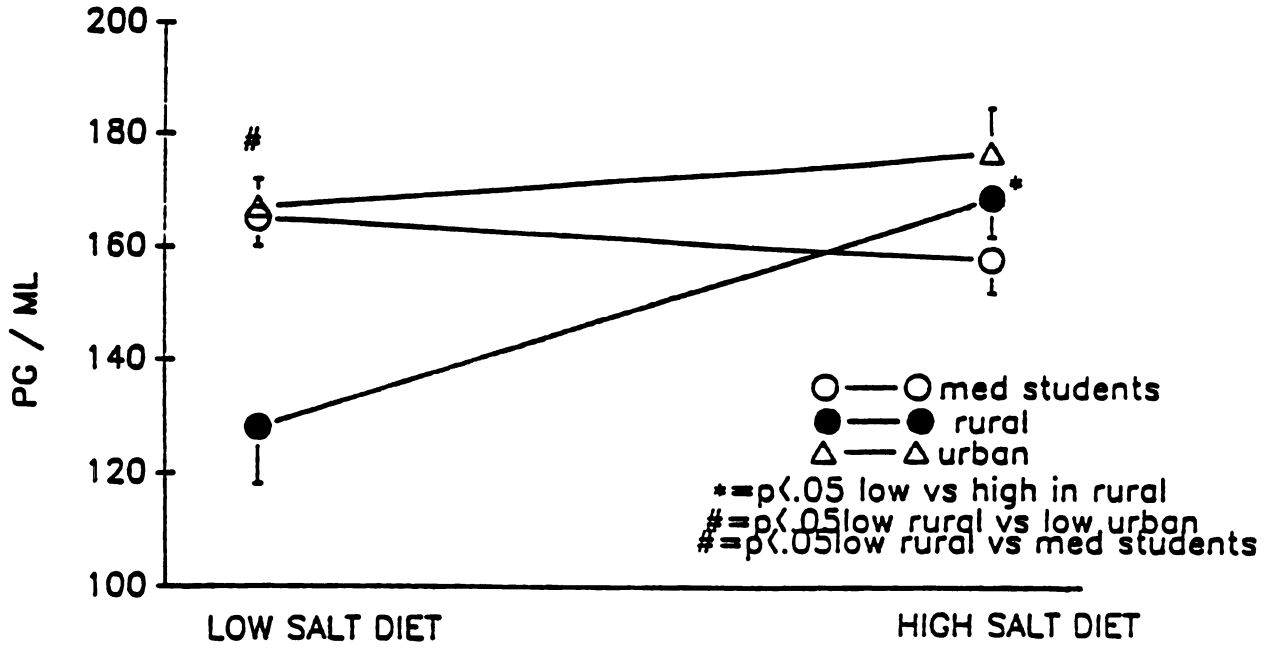


Figure 10. ANP response to dietary sodium in black men

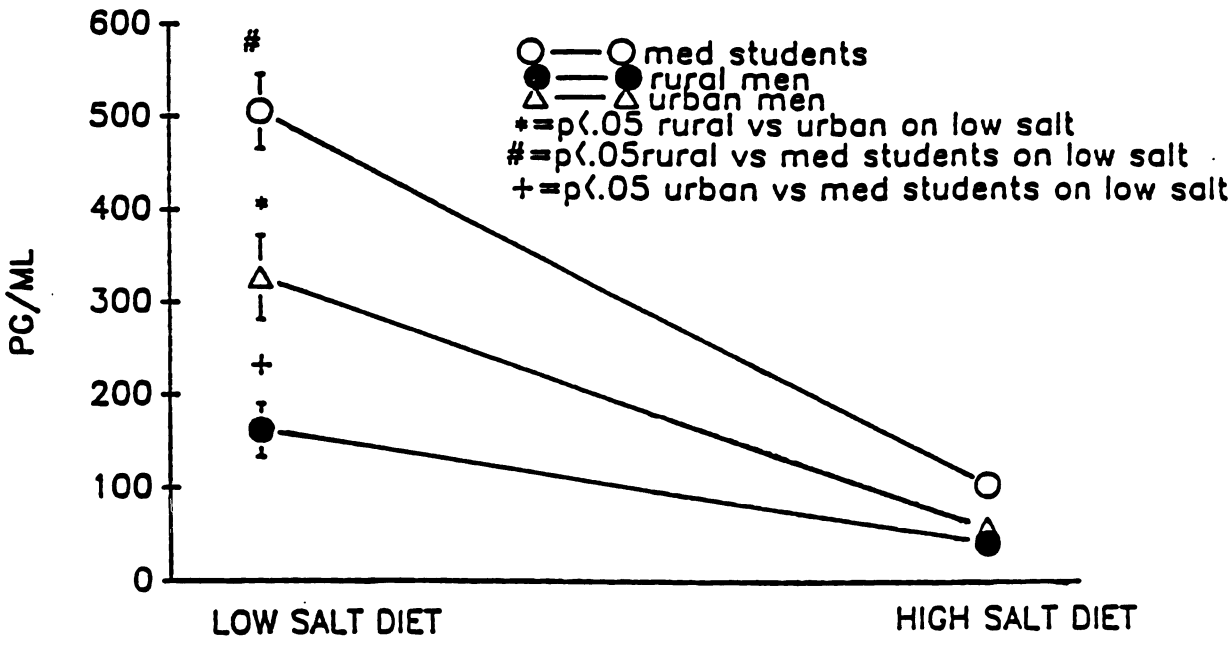


Figure 11. Aldosterone response to sodium in three groups of black men

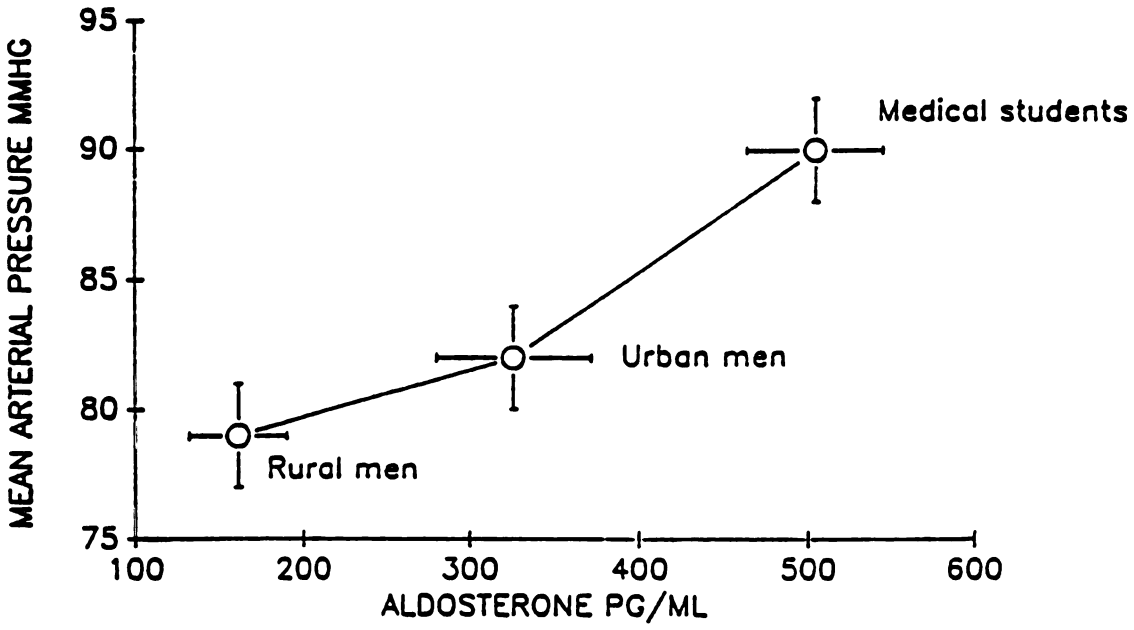


Figure 12. Interaction of pressure with aldosterone on low salt diet

DISCUSSION

Introduction:

Three major issues are addressed here. The influence of urbanization on blood pressure, the interaction of age and environment on blood pressure, and the influence of social class on blood pressure responses to dietary sodium chloride manipulation.

These subjects are presented in three parts. Data from medical students is discussed first. This is followed by a discussion of data from rural and urban men together. Urban men are contrasted with medical students. The influence of age is estimated from the comparison between low income urban men and the medical students. Data from rural and urban low income men is used to assess the impact of the environment. Medical students represent a high social class because of their western diet and because they can economically afford greater exposure to western influence.

Medical Students

Sodium Excretion

Control sodium excretion was quite high (247$\pm$14 mEq sodium/day)

compared with other population groups (Intersalt, 1988). These sodium excretion rates are similar to the highest reported in Intersalt study: a population of Northern China had an average intake of 246 mEq sodium/day. Some population groups excrete similar amounts of sodium and have increased mean blood pressures and higher prevalences of hypertension (Lot Page, 1982; Intersalt, 1988). We did not do a randomized survey rather we selected normotensives who were at risk of developing hypertension by nature of urbanization. The rationale of studying normotensives is to distinguish between cause and effect of hypertension. Hypertension may cause secondary metabolic changes through target organ damage, for example, sodium excretion may be altered because of nephroscelerosis. It would therefore be difficult to determine whether the observed abnormal sodium metabolism is the primary factor in causing hypertension or a secondary effect of hypertension. Studying normotensive subjects circumvents this problem because there is no hypertension to interfere with the observed sodium metabolism. But failure to obtain expected results in studies on normotensives may be because the normotensive population is a "selected " subset of the population which is resistant to the development of hypertension. Observations obtained in this normotensive group may reflect subjects who are resistant to hypertension rather than a "prehypertensive" stage (Kirkendall et al., 1975). The solution to this dilemma is to study subjects that are known not to be exposed to a particular hypertension stimulus. For example, the Yanomamo indians of Brazil or the highlanders of Papua New Guinea are not exposed to salt as a hypertension stimulus. Hypertension is absent in all surveys in these populations (Intersalt 1988). Studying these subjects on their normal

low sodium diet and on an experimental high sodium diet might reveal the extent to which sodium is contributory to the development of hypertension.

In our study, low salt diet was calculated to provide 10 mEq of sodium/day. The levels of sodium excreted by these subjects were similar to those reported for "low salt low blood pressure" populations (Lot Page, 1982; Intersalt, 1988). After four days of low salt diet, our subjects were nearly in sodium balance because the sodium intake was close to sodium excretion which was 23±2 mEq sodium/day. It had been shown earlier that it takes at least three days for people on a low salt diet to establish electrolyte equilibrium (Luft et al., 1979; Rikimaru et al., 1988). This value was similar to what other investigators have observed on this diet (Rikimaru et al., 1988; Luft et al., 1979; Lawton et al., 1986).

High salt diet was calculated to provide 800 mEq sodium/day. Urinary sodium excretion/day was 583±21 mEq. A number of possibilities can account for the sodium intake-urinary excretion difference. Fecal or sweat loss, and extracellular fluid and bone retention of sodium are all plausible explanations.

Sodium Intake

Food was weighed before consumption and the leftovers were weighed so that the actual amount of food eaten was known. The amount of sodium in the raw food was calculated from standard food tables for locally available foods (Chitsiku, 1981). The amount of sodium added to food during preparation was weighed. Additional sodium, taken orally as tablets made the total sodium intake 800 mEq/day. The tablets were

consumed under supervision during meal times. As a result, the sodium intake in our subjects was known precisely.

Non Urinary Sodium Loss

The fecal or sweat loss was not measured in this study. Reports in which fecal sodium loss has been measured have consistently found fecal sodium loss to be much less than 10% of the sodium intake (Kirkendall et al., 1975; Rikimaru et al., 1988). The fecal loss does not therefore, appear to contribute much to the observed deficit between sodium intake and urinary excretion.

Body Sodium Retention

Body weight increased from 65±2 kg on control diet to 6812 kg on high salt diet. Because body sodium is largely confined to the extracellular space (ECFV), we can safely assume that this was mainly increased ECFV. The plasma concentration of sodium did not change significantly on the three sodium diets. Three liters of interstitial fluid weigh about 3 kg. The sodium concentration in interstitial fluid was 140 mEq/liter. Body retention alone can account for (140 x 3) 420 mEq of sodium/4 days or about 100 mEq sodium/day.

Sodium Balance after Four Days:

Sodium urinary loss in four days was (582 mEq x 4 days) 2328 mEq. Sodium retained in the body in four days was 420 mEq. Urinary sodium loss plus sodim retained in the body retained sodium was 2748 mEq. Sodium intake in four days was (800 mEq x 4) 3200 mEq. Sodium that was not accounted for was 452 mEq.

The most likely explanation for the discrepancy between intake and urinary excretion of sodium is that, 113 mEq of sodium/day was lost through the fecal or sweat routes. This comprises a loss of 14% of intake. This is quite consistent with other results (Burstzyn et al., 1980; Kirkendall et al., 1975).

Potassium Excretion

There was kaliuresis on the high salt diet. This kaliuretic effect of sodium load has been reported in some studies (Luft et al., 1979; Kirkendall et al., 1975) but not all (Burstzyn et al., 1980). The significance of increased urinary potassium excretion as sodium intake, retention, and excretion increase is not known (Gamble and Wallace, 1951). Carcass studies of the effect of chronic salt ingestion on potassium content in rats revealed no significant differences in potassium between rats given low and high salt diets. Further, in a human study, there was no change in exchangeable potassium in normotensive subjects after 4 weeeks on a 410 mEq sodium/day or 10 mEq sodium/day (Kirkendall et al., 1975). In our study, the the increased potassium excretion occurred at a time when plasma renin activity and plasma aldosterone were relatively low. Thus it is that these endogenous humoral agents were responsible for the potassium behaviour.

Potassium Balance

Potassium supplementation enhanced kaliuresis in these subjects. Potassium excretion was 196 mEq for the group on high sodim with potassium supplementation. For the group that did not have supplemental potassium excretion was 112 mEq/day. Calculated potassium intake was

100 mEq/day.

The difference between the two groups was 84 mEq/day which is 16 mEq less than the potassium intake. Plasma potassium concentration did not significantly change from the control value of 4.5 mEq/liter.

The body weight increase of 3 kg can account for an increae of ECFV potassium of 13.5 mEq in four days.

Potassium supplemented was (100 mEq x 4)	400	mEq
Potassium urinary excretion was (84 mEq x 4)	336	mEq
Potassium retained in body was	13.5	mEq
Potassium retained and excreted in urine was	349.5	mEq
Potassium that cannot be accounted for was	50.5	mEq or

12.6 mEq/day or 12.6% of potassium intake. Potassium may have entered the cell but intracellular potassium was not measured in our study. The ratio potassium excreted to potassium taken in was quite similar to that calculated for sodium. Hence the sodium and potasssium which are not accounted for may have been lost by similar routes i.e., fecal and sweat.

Blood Pressure Responses

There is no standard definition of sodium sensitivity. The most commomnly used and the one we used in our study is a statistically significant increase in mean arterial pressure from a 10 mEq sodium diet to an 800 mEq sodium diet (Falkner 1988). Our subjects were not sensitive to the pressor effects of sodium. Systolic blood pressure significantly increased from low salt diet to high salt diet. Diastolic pressure significantly decreased from low to high salt diet. Mean arterial pressure did not significantly change from low salt to

high salt diet. These results were similar to those in whites studied by Kirkendall et al (1975).

Kirkendall et al. (1975) studied 8 white male normotensive prisoners on 3 levels of sodium intake. They were on 10, 210, and 410 mEq sodium/day each for 4 weeks (total 12 weeks). Blood pressure did not change. The authors suggested that sodium load did not affect blood pressure because either the stimulus for blood pressre to increase was not applied for long enough or the subjects were relatively salt resistant. Their basis for inadequate duration of the sodium pressor stimulus comes from the fact that western societies are subjected to high salt intake from childhood but only develop hypertension in their fourth decade of life. In addition, among the nomadic Samburu warriors, who entered the Kenyan army and changed from a low salt diet to a relatively high salt diet, there was no significant change after 6 months of exposure but blood pressure significantly increased after 2 years (Shaper and Saxton, 1969). This suggested that, if salt intake played an etiologic role in hypertension it would be a delayed one. Failure of blood pressure to increase in these subjects may be related to the fact that they were prisoners and were already stressed. Stress is another proposed stimulus for development of hypertension (D. Simmons et al., 1988). Since the authors selected normotensive subjects who were under the stress of being prisoners, they may have selected individuals with a low susceptibility to develop hypertension (Kaminer et al.,). They may have been resistant to the hypertension inducing characteristics of both stress and high salt which characterize western society. If this is true, salt load would not be expected to increase blood pressure of these subjects.

Burstzyn and co-workers (1980) failed like we did, to show a hypertensive response to salt in a group of whites in England who they fed a diet with sufficeient sodium to treble sodium excretion.

Potassium supplementation did not significantly alter blood pressure in our subjects. This is not surprising.
Burstzyn and colleagues (1980) found potassium supplementation not hypotensive in 20 normotensive subjects on high salt diet. However, these researchers did not observe increase in blood pressure due to the sodium load. This adds another possible dimension; that the depressor effect of potassium not only depends on the presence of sodium load but also on the sensitivity to the pressor effect of sodium.

Hormone responses

Plasma aldosterone concentration increased significantly from control to low salt diet. The plasma concentration of aldosterone in our subjects on low salt diet was similar to that reported in other sodium restriction studies (Skrabal, 1980; Luft, 1979; Kawasaki, 1985). The Yanomamo Indians, who are a low salt population group, (Oliver et al., 1975) excreted equivalent amounts of sodium on a lifetime basis and had aldosterone levels that were similar to those in our subjects on the low salt diet. This observation helps validate the use of acute dietary studies and the acute hormone and blood pressure profiles which occur in response to acute diet manipulation to represent lifetime processes (Oliver et al., 1975).

Plasma aldosterone decreased significantly from low salt to high salt diet. Potassium supplementation on high salt diet tended to increase aldosterone levels but this was not significant.

Potassium increases aldosterone production by directly stimulating the zona glomerulosa cells (Haddy et al., 1988).

AII levels were not significantly different between control and low salt diet in our subjects. AII is the active product of plasma renin activity. Renin secretion from the juxtaglomerular cells is reflexly stimulated by volume depletion, and directly low renal artery pressure or by reduced filtered sodium load. Prorenin is activated by tissue kallikrein to form active renin. Active renin clips off a decapeptide from renin substrate, angiotensinogen. This peptide is angiotensin I. Converting enzyme or Kininase II, secreted primarily by the lungs but also by endothelial cells elsewhere, clips off two amino acids to leave AII, the most active endogenous vasoconstrictor known (Inagami et al., 1988). AII stimulates aldosterone production and sympathetic activity. These mechanisms enable preservation of blood volume and adequate tissue perfusion.

AII levels were significantly higher in subjects on both control and low salt diet than high salt diet. This reduction in AII on high salt was not significantly influenced by potassium supplementation. The mechanism responsible for the lower AII on high salt diet appears to be related to reduction in plasma renin activity which is associated with increased filtered sodium.

Rural and Urban Men

Sodium Excretion

The sodium excretion in the rural and urban men did not differ on the control diet. Both groups of men consumed food that we prepared

while they were on control diet. Subjects had free access to salt. However, the salt added to the food during preparation may not have been comparable to what these subjects would consume at home.

We did not ascertain whether our subjects had free access to salt in their home environment. In our study, the convenience of having our subjects stay in a central location and eat the same food allowed maximum compliance which outweighed the advantage of a genuine home diet which would have been uncontrolled. 24 hour urine collection at home might have been frought with problems like incomplete collection or mixed urine samples. Failure to collect urine might have occurred because of inaccurate perception of 24 hours or the social inconvenience of carrying urine bottles in the public. Intersalt (1986) used home collected urine samples and relied primarily on stressing to the subjects both verbally and in writing, the significance of a complete collection of urine. In addition, Intersalt used 24 hr creatinine excretion as an index of completeness of urine collection. The control sodium excretion for our urban and rural men of 130$\pm$15 mEq and 142$\pm$10 mEq sodium/day are similar to 141+8 mEq sodium/day in 200 urban Zimbabweans who participated in Intersalt (1988) and to those reported in most western surveys (Lot Page, 1982).

Urinary excretion of sodium on the high salt diet was markedly different from the calculated intake. The weight increased from 55+1 kg on control diet to 59+1 kg on high salt in the rural men and from 62+2 kg on control to 68+2 kg on high salt in the urban men. If we make similar assumptions as for the medical students we get the following:

Rural Men

Sodium urinary excretion was (402 mEq x 4)	1608 mEq
Sodium body retention was (140 mEq x 5)	700 mEq
Sodium retained and excreted in urine was	2308 mEq
Calculated sodium intake was (800 mEq x 4)	3200 mEq
Sodium that cannot be accounted for was	892 mEq
Sodium non urinary loss/day was (28% of intake)	223 mEq

Urban Men

Sodium urinary excretion was (513 mEq x 4)	2052 mEq
Sodium body retention was (140 mEq x 6)	840 mEq
Sodium retained and excreted in the urine was	2892 mEq
Calculated sodium intake was (800 mEq x 4)	3200 mEq
Sodium that cannot be accounted for was	308 mEq
Sodium non urinary loss/day was (10% of intake)	77 mEq

The urban men behaved more like medical students than did the rural men. There was increased non urinary loss of sodium in rural men compared to urban men. The route of nonurinary sodium loss was not ascertained in this study.

Possible Explanations for Positive Electrolyte Balance

The failure of electrolyte intake to match urinary excretion has already been discussed (Luft et al., 1979; Bursztyn et al., 1980; Kirkendall et al., 1975). The deficit was more marked in the rural men who excreted 50% of sodium intake in the urine after 4 days of high salt diet. The explanation for the deficit between sodium intake and urinary sodium excretion has not been clearly established. Noncompliance among

the subjects for example, not eating the food correctly was not likely because the subjects were well supervised throughout the study. One of the investigators was always present at meals and assured that the sodium tablets were taken. The subjects were repeatedly instructed on how to perform the 24 hour urine collection. The rural subjects were confined to the experimental site during the collections. In addition, the creatinine excretion coefficients were all within normal range for complete 24 hour urine collection as shown in Table 4.

If all the sodium not accounted for by urinary excretion had been retained in the body fluid, marked body weight with considerable accumulation of water would have been observed. Weight gain can account for 700 mEq sodium. The unccountable sodium was 1600 mEq. Possible explanations for the apparent positive sodium balance observed in the rural subjects are loss of sodium in perspiration, or deposition somewhere other than in extracellular fluid such as intracellular space, bone, or tissue solid. Our study was conducted during the cool months of the year, August and September which minimized sweat losses. In addition, the subjects engaged in limited physical activity so that sweating was minimized.

Sweat and Fecal Electrolyte Loss

Streeten et al. (1962) studied sweat loss in normal humans. Subjects continued to use the same clothing and bed clothes and wore plastic bags around socks to trap foot sweat. They washed only their faces and hands each day with cloths and water which were saved for analysis. At the end of the week, the subjects were carefully washed in big volumes of distilled water in a tub in which all the clothing,

pillowcases, sheets, towels, and wash cloths were subsequently washed and immersed for several hours. Sodium was then measured. Sodium was also measured in all the feces that were produced during the week. Sweat loss and fecal sodium loss combined was less than 4.4 mEq/day.

However, Conzolazio et al. (1963), reported that humans lost 26 mEq sodium/hour at 37^{o}C through perspiration. Hence this route of sodium loss is not negligible under conditions of heat stress. The fecal sodium loss estimate by Streeten et al. above, was done on control diet. Rikimaru et al. (1988) measured fecal sodium loss in Papua New Guinea highlanders on both control and high sodium diet and found that the sodium loss was less than 10% of the calculated intake. This study suggests that fecal loss of sodium may not have been a significant factor in accounting for the sodium deficit in our study..
It is therefore still uncertain what became of sodium which is not accounted for.

Bone in Electrolyte Storage

There is some evidence that bone serves as a sodium and potassium reservoir. The total human body sodium content of the adult human has been found by carcass analysis to lie between 57 mEq/kg and 73mEq/kg body weight. Of this sodium approximately 30 mEq/kg is known to be contained within extracellular fluid where it is freely and rapidly exchangeable. The remaining 30 mEq sodium/kg body weight is bone sodium. In normal adults, a certain amount of bone sodium has been shown by direct measurement to exchange freely with radiolabelled sodium within 24 hours (Streeten et al., 1962). Patients with primary aldosteronism exhibit smaller amounts of this slowly exchangeable pool

of body sodium. The suppression of aldosterone by high sodium intake would conceivably cause increase in exchangeable body sodium pool and thus cause sodium retention and could possibly account for the sodium deficit which we observed between intake and urinary excretion in our rural subjects.

Furthermore, intracellular sodium is increased in some essential hypertensives (Haddy, 1988). The mechanism involved is probably related to the chemically still indistinct sodium pump inhibitor found in most essential hypertensives. Increased intracellular sodium has been demonstrated in sodium sensitive hypertensives (Blaustein et al., 1984). If the sodium sensitivity displayed by our subjects was associated with increased intracellular sodium, then the intracellular space could have acted as another pool of sodium which contributed to the positive sodium balance observed on the high salt diet in our subjects. It is also possible that chronically low sodium in rural subjects means their bone stores have little sodium and when exposed to sodium it goes into their bones.

A limitation of urinary osmolarity was unlikely the explanation for the sodium balance. The urine osmolarity increased from 400+37 mOsm on control diet to 537+30 mOsm on high salt. The urine osmolarity on high salt was less than 1000 mOsm when normal kidneys can excrete up to 1400 mOsm. There was no reason to believe that these subjects could not have excreted more sodium because of an osmotic limitation.

Plasma Aldosterone Response

The decrease of plasma aldosterone with sodium loading observed in both groups in this study is consistent with reports in the literature

on this subject (Luft et al., 1979; Dahl et al., 1962; Rikimaru et al., 1988). The increase in aldosterone with sodium depletion in the hospital workers is equally consistent. The aldosterone concentration tended to increase in our rural farmers but this did not reach statistical significance. This low aldosterone concentration for rural men was significantly higher than the the control aldosterone concentation of the urban men. This is because control aldosterone for the rural men tended to be higher than that of the hospital workers but this was not significant. The failure of aldosterone to increase significantly in the rural men is surprising.

The level of low salt aldosterone found in our rural subjects is similar to levels found in other populations living traditionally (Rikimaru et al., 1988). In the study by Rikimaru et al., the subjects decreased their aldosterone on high salt just like our subjects did. However, these subjects had been on a low salt diet for life as they did not add salt to their food. One obvious similarity between our rural subjects and these highlanders is they are both rural. A number of possibilities, none of which were investigated in this study, could explain some of these discrepancies. For example, first, dietary lipid, the source of aldosterone substrate may be limiting in our population, and second, the rural subjects may exhibit low renin activity which would limit AII production which is a potent aldosterone stimulus and finally the rural subjects may exhibit adrenal hypofunction which would limit responses to adrenal secretions in general. Other secretions of the adrenal gland were not measured. All these three parameters need to be investigated in the future in order to be able to identify the explanation for this abnormal adrenal response and its

possible clinical implications. Clearly further work needs to be done to clarify this difference in adrenal response to sodium restriction in the two environments.

ANP Response

Our results failed to demonstrate significant increase in ANP from control salt to high salt diet in both groups of low income men. We were able to show that the rural men exhibit the suppression of ANP and did not increase aldosterone on low salt diet which was different from urban men and indeed different from most other reports. Because of the uncertain role of ANP in normal sodium homeostasis, caution must be exercised in the interpretation of these data, but they are consistent with renal salt conservation by lowering ANP instead of by raising aldosterone.

A wide range of plasma ANP from 3 pg/ml to 900 pg/ml have been reported in the literature by different groups. The values reported here are in the middle range and other groups have reported levels that were very similar to ours (Tang et al., 1985; Sugawara et al., 1985; Miyamuri et al., 1987). The difference in the ANP levels reported in different laboratories may be related to the content of sodium in the diet, the posture of the subjects when the blood is taken, use and concentration of protease inhibitors, temperature control from specimen collection to gamma counting, extraction procedure and extraction efficiency, and the radioimmunoassay procedure. There is to date no standard way of doing any of the above (Tang et al., 1985).

We employed the direct, (without extraction) assay of ANP as do most other laboratories (Tang et al., 1985; Shenker et al., 1985; Morris et

al., 1987; and Richards et al., 1987). Direct radioimmunoassay of plasma is very accurate as demonstrated by Morris et al. (1987) and Richards et al. (1987). The validity and precision of the direct assay was shown especially well by Morris et al. They demonstrated parallelism of the standard curve and with serial dilutions of plasma samples as well as close agreement between ANP concentration obtained directly and from extracted plasma. In our direct assay samples of pooled human plasma were assayed as a control. In addition we added known amounts of standard ANP to the pooled plasma samples (spiked samples). Recovery of ANP from the spiked samples was 98+10% for the three groups.

In other studies, consumption of a high salt diet has been associated with different degrees of change in plasma ANP concentration. In our urban men, there was no significant change in the ANP concentration but our rural subjects displayed a significantly lower ANP on the low salt diet than on the control or high salt diet. There was no significant change between control and high salt diet in either rural or urban men. This failure of ANP to increase from control to high salt diet suggests that ANP may not be important in steady state sodium metabolism in our population and may not be related to the differences in blood pressure prevalences in rural and urban Zimbabwe.

The failure of ANP increase with increase in dietary sodium is surprising but has been observed before. Saville et al. (1988) failed to show ANP increase with a high sodium diet administered to subjects who were either in supine or in upright posture. They also demonstrated that sodium excretion increased when the subjects were on the high sodium diet although plasma ANP did not increase. These investigators also concluded like we did, that because natriuresis does not parallel

changes this hormone does not contribute to sodium homeostasis in black subjects.

The most potent stimulus for ANP release is atrial stretch (Tang et al. 1987). Supine posture has therefore been associated with higher levels of ANP than upright posture. In one study, Hollister et al. (1986) demonstrated that the postural effect was able to override the effect of sodium load on ANP release. These researchers observed marked attenuation of ANP increase stimulated by sodium when their subjects were upright compared to when they were position. Our ANP levels were only measured with the subjects in upright posture which may explain why plasma ANP concentration did not parallel changes in sodium excretion in our study.

Intracellular Sodium and Hypertension

More than 30 years ago, H. Losse et al. documented that sodium content was elevated in erythrocytes from subjects with essential hypertension. Erythrocyes were used for this particular study because they are easily accessible in humans. The assumption is that what happens in these cells also happens in vascular smooth muscle cells. Two to three mls of blood are withdrawn by venipuncture and transferred to heparinised tubes. Erythrocytes are separated from plasma by centrifugation and hematocrit is established in the process. Plasma is then discarded and the cells are washed with isotonic magnesium chloride. Osmotic hemolysis of the erythrocytes releases intracellular sodium and potassium. The ions can then be measured by flame photometry. Using this procedure, several laboratories (Blaustein, 1977; Haddy,

1981; Losse 1981; Garay, 1981; DeWardener and MacGregor, 1982) have also found differences among the ion content of erythrocyte from subjects with different types of hypertension and from different racial groups.

Losse et al. (1981) demonstrated that intraerythrocyte sodium was increased in erythrocytes of essential hypertensives compared to erythrocytes from normotensives or secondary hypertensives. Intra-erythrocyte sodium concentration was higher in blacks than in whites whether they were normotensives or hypertensives (Garay et al., 1981, M'Buyamba-Kabanguet et al., 1984). M'Buyamba-Kabangu et al demonstrated that intraerythrocyte sodium content was higher in cells from Zairean blacks who had migrated to Belgium than it was in cells from whites in Belgium.

The increased intra-erythrocyte sodium concentration can result from reduced sodium potassium pump activity, reduced outward sodium-potassium cotransport or increased passive permeability to sodium. Observation of abnormalities of these mechanisms may result in the increased sodium in these cells. R. Garay et al., (1981) studied the racial difference in intra-erythrocyte sodium tansport among both normotensive and hypertensive French whites and Senegalese blacks. Outward sodium-potassium cotransport was higher in white essential hypertensives than in white normotensives and it was even higher in black hypertensives than white hypertensives.

Whatever the primary mechanism for the increased intracellular sodium concentration in hypertension in erythrocytes, this defect appears to contribute to observed increased total peripheral resistance in hypertension. Blaustein et al. (1977) hypothetically linked sodium-calcium exchange to hypertension. According to the

sodium-calcium countertransport hypothesis, the increase in intracellular sodium would be translated into an increased intracellular calcium concentration. Part of the calcium transport out of the resting cell is by way of the countertransport carrier which depends energetically on the influx of sodium down its electrochemical gradient. Therefore, an increase in intracellular sodium would lead to an increase in intracellular calcium by decreasing the sodium gradient. This would decrease the rate of calcium efflux from the cell. In support of this relationship among sodium, calcium and hypertension is the observation by Oshima et al. (1988) that intracellular calcium is elevated in salt sensitive hypertensives when they are on high sodium diet. These researchers studied 12 moderately hypertensive subjects after stabilizing blood pressure and sodium balance on 10 g salt/day. Subjects received 3 g of salt/day for 7 days followed by 20 g of salt/day for another 7 days. Mean arterial pressure significantly incrased on the high salt diet. Calcium excretion significantly increased and total serum calcium decreased as compared to the low salt diet. Quin 2, a fluorescent calcium sensitive tetracarboxylate dye which has been developed to monitor stimulus coupled changes in calcium in several mammalian cells (Tsien et al., 1982), was used to measure intracellular calcium concentration in cells from these subjects. The hypotensive effect of nifedipine, a calcium channel antagonist, was correlated with reduced intracellular calcium after sodium loading. They concluded that salt sensitivity is mediated by increased intracellular free calcium. The assumption is that this increased intracellular calcium measured in lympocytes also occurs in vascular smooth muscles.

We did not measure intracellular free calcium but we did observe

calciuresis. It is therefore feasible that the observed sodium sensitivity in our subjects was also mediated by increased intracellular calcium. We regard this to be a critical factor to investigate in the future.

Another potential explanation for the pressor effect of salt is an increase in sympathetic nervous system activity. The firing rate of sympathetic neurons increases during the developmental phase in SHR fed a high salt diet compared with age matched rats fed low or basal salt diets (Dietz et al., 1980). Dietz et al. observed increased plasma and urinary norepinephrine and an exaggerated depressor response to ganglionic blockade in high salt fed SHR. In addition, the increase in plasma norepinephrine in salt loaded rats, is exaggerated during cold stress test. These findings suggest that, in the developmental phase of hypertension in SHR, increased sympathetic nervous system activity sets off a chain of events that leads to systemic hypertension. SHR maintained on 8% salt diet for two weeks displayed significant decreases in norepinephrine stores in the anterior and posterior hypothalamus but not in other hypothalamic or brainstem areas compared with rats maintained on 1% salt diet (Wyss et al., 1987).

Chen et al. (1988) confirmed that increased salt intake increases blood pressure in SHR but not in WKY and secondly that the sodium salt induced hypertension in SHR was associated with decreased norepinephrine stores and turnover in the anterior hypothalamus. The anterior hypothalamus is a region that mediates depressor responses and suppresses central sympathetic outflow when chemically or electrically stimulated. In addition, norepinephrine stores in the medulla and spinal cord of salt fed SHR were greater than in control WKY rats. These

findings are consistent with the hypothesis that salt loading exacerbates the severity of hypertension in SHR by decreasing the synthesis of norepinephrine or the release of norepinehprine from noradrenergic terminals in the anterior hypothalamus. Either would increase the release of norepinephrine from terminals in cardiovascular control centers in the brain stem.

In addition, Koepke et al. (1988) determined the responsiveness of central alpha 2 adrenergic receptors by comparing the dose response curves for the effects of cumulative intracerebroventricular injections of guanabenz, an alpha 2 agonist, like clonidine, on changes in mean arterial pressure, renal sympathetic activity, and urinary sodium excretion between SHR and WKY rats. High sodium chloride intake shifted the guanebenz renal sympathetic activity curve the guanebenz urinary sodium excretion curve to left in SHR and to the right in WKY. The dose response curves and blood pressure were similar for SHR and WKY rats on control salt. They concluded that the responsiveness of central nervous system alpha 2 adrenergic receptors is increased by increased salt intake in conscious SHR but not in WKY rats. Increased intracellular sodium and calcium have already been suggested as a common pathway for all the proposed mechanisms. Increased intracellular calcium increases the uptake and binding of norepinephrine by nerve endings and also causes increased release of catecholamines from nerve endings and the adrenal medulla (Keen and Bogdanski, 1970).

The other mechanisms that have been proposed to link sodium to the sympathetic nervous system and the pathogenesis of systemic hypertension include; alterations in baroreceptor sensitivity, vascular reactivity to alpha adrenergic agonists, sensitivty of presynaptic and postsynaptic

mechanisms that govern the release of and reuptake of biogenic amines and the synthesis, storage, and turnover of biogenic amines in central and peripheral neurons (Oparil, 1986). Clearly more studies need to be done to ascertain at the molecular level the involvement of sodium with the sympathetic nervous system activity to enable efficacious therapy and possble prevention of sodium dependent hypertension.

In addition to the humoral sodium pump inhibitor and and disinhibition of sympathetic output from the anterior hypothalamus, there is evidence for two other independent mechanisms that may link sodium to hypertension. Chen et al. (1988) demonstrated abnormal ANP regulation in SHR. They fed 7 week old SHR and WKY rats 1% and 8% sodium chloride diets for 2 weeks. The 8% salt diet increased blood pressure in SHR but not in WKY rats. Plasma ANP levels were significantly higher in WKY fed 8% salt than WKY fed 1% salt. Plasma ANP did not differ between the SHR and WKY on the 1% salt diet. 8% salt diet did not increase ANP in SHR. The observation that dietary sodium chloride stimulated ANP release in WKY rats and not in SHR suggests that the exacerbation in hypertension seen in salt loaded SHR may be related to an impairment in ANP release. In addition, ANP stores were elevated in the anterior hypothalamus of SHR fed either diet diet compared to WKY. The role of this alteration in central nervous system ANP in the pathogenesis of sodim chloride sensitive hypertension remains to be determined. While the relevance of these observations in SHR to studies in normotensive humans are unclear, the failure for ANP to increase in our subjects on high sodium chloride diet may be due to a similar mechanism. But because we do not have data from both normotensive and hypertensive subjects, it is difficult to compare our human data to the

SHR and WKY data.

Another possible explanation of salt sensitivity is a difference in the sensitivity of the renal circulation to salt in hypertensives. Lawton et al. (1988) studied normotensive and borderline hypertensive white males on 10 mEq and 400 mEq sodium diets. Standing up lowered diastolic pressure in the normotensives and in contrast did not change in the borderline hypertensives, but reduced renal plasma flow and increased renal vascular resistance to similar extents in both groups of subjects after 6 days of a low salt diet. Standing up significantly decreased renal plasma flow and increased renal vascular resistance index by 14% and 48% in the normotensive and borderline hypertensives respectively after 6 days of the high salt diet. Upright posture also reduced the free water clearance to a greater extent in the borderline hypertensives than in the normotensives. A high sodium diet appears to unmask an abnormality in the neurohormonal control of the renal circulation in borderline hypertensives which may contribute to the development of hypertension in these subjects who are at high risk for hypertension. Again we do not have any data concerning renal hemodynamics in our subjects and so cannot comment on the possibility that this type of mechanism could be working to cause salt sensitvity in them.

The Influence of Potassium Supplementation on Sodium Responses

Epidemiological evidence indicates that the increase in blood pressure and higher prevalence of hypertension in blacks than whites may be related to less dietary potassium and calcium intake in blacks than whites. In addition the the lower hypertension prevalences in

traditional societies has also been attributed to the higher potassium intakes in these societies. Lower dietary potassium provisions of urban populations culture have been suggested to contribute to the higher prevalence of hypertension associated with urbanization.

Potassium supplementation in our urban and rural men did not significantly alter blood pressure. Urinary potassium excretion was less than 50% of calculated intake. The explanation for this positive potassium balance was not investigated. Possibilities include fecal and sweat loss and body retention as already described for sodium.

Potassium supplementation approximately halved the sodium/potassium ratio on high salt from 12 to 6 in both groups of men. This ratio was still significantly higher than the control sodium/potassium ratio of 3 for rural and 4 for urban men. Sodium/potassium ratio has been shown to be a better predictor of blood pressure response than either sodium or potassium individually (Dahl et al., 1962). Probably a certain threshold level of this ratio is required to either increase or decrease blood pressure. Our subjects may have exceeded this threshold which caused blood pressure to be higher while potassium supplementation was not sufficient to decrease the ratio below the threshold for blood pressure increase. Other potassium intervention studies (Miller et al., 1987; Bursztyn et al., 1980) which increased potassium intake by more than 50% failed to decrease blood pressure in their normotensive subjects by increasing potassium intake by more than 50% of control intake. In addiition, Luft et al., who did show a protective effect of potassium in normotensives maintained a zero potassium balance by replacing the previous day's potassium excretion in the form of tablets. It is not possible to relate this zero potassium balance to

sodium/potassium ratio in the Luft study because the actual potassium excretion was not reported. It is likely that the potassium intake was high in this subjects, because the sodium load had produced kaliuresis which would have reduced the sodium potassium ratio.

Medical Students and the Low Income Urban and Rural Men

Electrolyte Excretion

Control sodium and potassium excretion were both higher in the medical students than in the two groups of low income men. The control sodium/potassium ratio was higher in the medical students and urban men than in the rural men. Among these three groups, except that they were selected because they had normal blood pressure, the higher sodium and potassium excretion rates in the medical students and the higher sodium/potassium ratios in the medical stucdents and in the urban men may indicate that the medical students and the urban men are at higher risk of of developing hypertension in the than thre rural men.

Cardiovascular Responses

Systolic blood pressure significantly increased when the subjects went from low salt to high salt in all the three groups of men. Diastolic pressure did not significantly change in the low income men but significantly increased when the medical students went from low salt to high salt. As a result, calculated mean arterial pressure significantly increased in the low income men and did not significantly change in the medical students from low salt diet to the high salt diet. On this basis, medical students were resistant to the pressor effects

of sodium compared to the low income men. Sensitivity to the pressor effects of sodium appears therefore to be age dependent in Zimbabwean men (Zemel et al., 1987). The explanation for the age dependency to the pressor effects of sodium could be localised in the kidney's inability to effectively excrete a sodium load as clearly demonstrated by Luft et al., (1980), who showed a decline in renal blood flow, and glomerular filtraton rate with age. In addition this age dependent decrement in renal function is more marked in blacks than whites.

Hormonal responses

We also demonstrated a decline in the renin angiotensin system reduction with age as estimated by plasma aldosterone. Plasma levels of renin and aldosterone decrease with age. This has been attributed to renal hypofuncton because other indices of adrenal function were not altered. Our results show that aldosterone on low salt diet was significantly higher in the medical students than in both groups of low income men which may be age dependent because the medical students were much younger than the low income men (Table 1). In addition, the aldosterone was higher for the urban men than for the rural men. The higher aldosterone for the urban men than for the rural men can not be explained by age difference because the subjects were age matched.

ANP increased when rural men went from low salt to to high salt. ANP did not change in urban men or medical students when they went from low salt to high salt diet. It is possible that rural men use a decrease in ANP rather than an increase in aldosterone to conserve sodium. This may possibly reflect the age related decrease in aldosterone secretion. Although the role of ANP in salt and water homeostasis is not yet clear,

these data are consistent with ANP suppression becoming the predominant mechanism of sodium retention to maintain blood volume and blood pressure with increasing age.

Conclusion

The working hypothesis for our medical student subjects was that Zimbabwean black men are as sensitive to the pressor effects of sodium as American black men. In addition, we proposed that this this pressor effect is attenuated by supplemental potassium. We were interested in this question because the increased sensitivity to the pressor effects of sodium may contribute to the reported high prevalence of hypertension in Zimbabwean urban black men which has already been shown in American blacks. Sodium significantly increased systolic pressure, decreased diastlolic pressure and did not significantly change mean arterial pressure in the medical students. Potassium supplementation did not alter this blood pressure response. These findings contrast with those in American blacks who significantly increased systolic, diastolic and mean arterial pressure when they went from low salt to high salt diet. We therefore rejected our hypothesis that Zimbabwean blacks are as sensitive to pressor effects of sodium as American blacks.

The resistance to the pressor effects of sodium in these students may be related to age in that they were younger and could compensate for the increase in body sodium by widening pulse pressure rather than increasing mean arterial pressure. In addition they were able to suppress their renin angiotensin system effectively.

The working hypothesis for our urban and rural subjects was, urban men are more sensitive to the pressor effects of sodium and this pressor effect is abolished by supplemental dietary potassium. We further proposed that this increased sensitivity to sodium contributes to the higher prevalence of hypertension in urban than rural Zimbabwe. Our data show that both rural and urban men are equally sensitive to the pressor effects of sodium. Sodium sensitivity does not therefore appear to contribute to the higher prevalence of hypertension in the urban than in the rural population in Zimbabwe. The demonstrated sodium sensitivity does not apprear to be related to an unusual response to ANP or to aldosterone. In addition, potassium supplementation does not alter the sodium pressor-sensitivity. The sodium pressor sensitivity in Zimbabwean men appears therefore to be age dependent.

We noticed that rural men release less aldosterone than urban men on the same level of sodium restriction and that aldosterone secretion is suppressed with increasing age. We did not establish whether this decrementin aldosterone production was of renal or adrenal origin.

The low income rural men had lower aldosterone and ANP on low salt diet compared to the other two groups. It is not clear whether the apparent suppression of ANP is a mechanism used by these rural subjects to conserve body sodium when aldosterone stimulation does not materialize. The rural men excreted a lower fraction of the sodium and potassium load than either the medical students or the urban men. The explanation for this inabilty to excrete sodium in these subjects was not investigated in these studies. The higher hypertension prevalence in urban than rural Zimbabwe needs to be further studied with closer scrutiny of dietary factors such as lipids, sugar and alcohol also

social factors such as stress and day to day lifestyle.

REFERENCES

Ahrens, R.A. Sucrose, hypertension and heart disease: an historical perspective. Am. J. Clin. Nutr. 27: 403-22, 1974.

Akinkugbe, O.O. and O.A. Ojo. Arterial pressures in rural and urban populations in Nigeria. Br. Med. J. 2: 222-4, 1969.

Akinkugbe, O.O. World epidemiology of hypertension in blacks. In: Hypertension in Blacks, Epidemiology, Pathophysiology and Treatment. Hall, Saundeers and Shulman (eds.), Year Book Medical Publishers, pp. 3-17, 1985.

Aksay, M.O., R.A. Murphy and K.E. Kamm. Role of calcium and light chain phosphorylation in regulation of smooth muscle. Am. J. Physiol. 242: C109-C116, 1982.

Anderson, D.C., W.D. Kearns, and W.E. Better. Progressive hypertension in dogs by avoidance conditioning and saline infusion. Hypertension 5: 286-91, 1983.

Anderson D., W. Kearns and T.Worden. Potassium chloride infusion attenuates avoidance-saline hypertension in dogs. Hypertension 5: 415-20, 1983.

Arkwright, P.D. Effects of alcohol use and other aspects of lifestyle on blood pressure levels and prevalence of hypertension in a working population. Circulation 66: 60-6, 1982.

Bauer J.and W. Gaunter. Effect of potassium on plasma renin activity and aldosterone during sodium restriction in normal man. Kidney International 15: 286-93, 1979.

Belizan R. Reduction of blood pressure with calcium supplementation in young adults. J.A.M.A. 249: 1161-65, 1983.

Bergstrom W. and W. Wallace. Bone as a sodium and potassium reservoir. J. Clin. Invest. 867-73, 1954.

Best, J.B., J.P. Coghlan, J. Bett and J. Cran. Circulating AII and aldosterone levels during dietary sodium restriction. Lancet 2: 1353-54, 1971.

Bjorntorp, P. Obesity and the risk of cardiovascular disease. Ann. Clin. Res. 17: 3-9, 1985.

Blaustein, M.P. Sodium ions, blood pressure regulation and hypertesion: A reassessment and a hypothesis. A.J.P. 232: C165-C173, 1977.

Blaustein, P.M. Commentary: What is the link between vascular smooth muscle sodium pumps and hypertension? Clin. Exp. Hypert. 3: 173-8, 1981.

Blaustein, P.M. and J.M. Hamlyn. Role of a natriuretic factor in essential hypertecnsion. Ann. Intern. Med. 989: 785-92, 1983.

Brown, J.J., A.F. Lever, J.J. Morton, R. Frase, D. Love and J. Robertson. Increased plasma angiotensin II and aldosterone during dietary sodiuun restriction in man. Lancet 1106-7, 1972.

Brunner H. R., L. Baer, and J. E. Sealey. The influence of potassium administration and of potassium deprivation on plasma renin activity in normotensives and hypertensives. J. Clin. Invest. 49: 2128-38, 1970.

Bursztyn, P.G. and D.R. Husbands. Fat induced hypertension in rabbits. Cardiovasc. Res. 14: 185-91, 1978.

Bursztyn, P., D. Hornall and C. Watchdon. Sodium and potassium intake and blood pressure. Brit. Med. J. August 1980.

Bursztyn, P. A diet survey in Zimbabwe. Human Nutr.: Appl. Nutr. 39A: 376-88, 1985.

Bursztyn, P.G. Alcohol and Blood pressure: a social comparison in Zimbabwe. Postgrad. Med. J. 62: 1011-16, 1986.

Burton, B.T. Health implications of obesity: an NIH consensus development conference. Int. J. Obesity 9: 155-69, 1985.

Campbell W. and J. Scmitz. Effect of alterations in dietary potassium on pressor effects and sterodogenic effects of AII and AIII. Endocrinology 103: 2098-2104, 1978.

Chen, Y.F., Q. Meng, M. Wyss, H. Jin and S. Oparil. High sodium chloride diet reduces hypothalamic norepinephrine turnover in hypertensive rats. Hypertension 11:55-62, 1988.

Chiang, B.N. Overweight and hypertension. Circulation 39: 403-21, 1969.

Chitsiku I. C. Nutritive value of foods of Zimbabwe. Bulletin number 104, dept of Food and Nutrition, Ames, Iowa, 1981.

Clark C. Effects of various factors in the Los Angeles heart study. J. Chr. Dis. 35: 879-86, 1967.

Cohen, L.S., D. Jhetam, J. Da Silva, F. Milner and A. Walt. Sodium and potassium status, plasma renin and aldosterone in normotensive and hypertensivecJohanesburg Blacks. S. Afr. Med. J. 62: 941-4, 1982.

Cooper R., N. Shamsi and S. Katz. Intracellular calcium and sodium in hypertensive patients. Hypertension 9: 224-9, 1987.

Crane, G.M. and J.J. Harris. Effect of aging on renin activity and aldosterone excretion. J. Lab. Clin. Med. 87: 947-59, 1975.

Dahl, L. and D. Love. Evidence for the relationship between sodium chloride intake and human essential hypertension. Arch. Int. Med. 94: 525-31, 1954.

Dahl, L.K. Evidence for an increase intake of sodium in hypertension based on urinary excretion of sodium. Proc. Soc. Exp. Biol. Med. 94: 23, 1957.

Dahl L., M. Heine, and L. Tassinari. Effects of chronic excess salt ingestion: Evidence that genetic factors play an important role in susceptiblity to experimental hypertension. J. Exp. Med. 115: 1173, 1962.

Dahl, L., G. Leitl and M. Heine. Influence of dietary potassium and sodium/potassium ratio on development of salt hypertension. J. Exp. Med. 138: 318-30, 1972.

Diertz R. Partial replacement of sodium by potassium in the diet lowers blood pressure in stroke prone SHR. Clin. Science 61: 69s-71s, 1981.

Dietz, R. and A. Schomig. Enhanced sympathetic activity caused by salt loading in SHR. Clin. Sci. 59: 171s-173s, 1980.

Donnison, C.P. Blood pressure in the African Native. Lancet 1: 6-7, January 1929.

Dyer, A.R., Stamler J., R. Shelkelle and J. Schoenberger. The relationship of education to blood pressure: Findings on 40,000 employed Chicagoans. Circulation 54(6): 987,1976.

Edwards, O.M. and R.I. Baylis. Urinary creatinine excretion as an index of the completeness of 24 hour urine collection. Lancet 2: 1165,1969.

Edwards, B.S., R.S. Zimmerman, T. Schwab, D. Heublin and J. C. Burnett. Atrial strecth, not pressure is the principal determinant controlling the acute release of ANP. Circulation Res. 62(2): 191-5, 1988.

Falkner, B. Sodium sensitivity: a determinant of essential hypertension. J. Am. Coll. Nutr. 7(1): 35-4, 1988.

Fisch W. and W. Frank. Oral contraception and blood pressure. J.A.M.A. 237: 2499-2503, 1977.

Forsyth F. Hypertension in Tanzania, Preliminary Communication. East Afr. Med. J. 46(5): 309-12, May 1969.

Friedman, R. and L. Dahl. The effect of chronic conflicts on the blood pressure response of rats with a genetic susceptibilty to experimental hypertnsion. Psychosomatic Med. 37 (5): 402, 1975.

Fujita R. Factors influencing blood pressure in salt sensitive patients with hypertension. Am. J. Med. 69: 334-344, 1980.

Garay, P.R., C. Nazaret, G. Dagher, E. Bertrand, and P. Meyer. A genetic approach to the geography of hypertension: Examination of sodium-potassium cotransport in Ivory Coast Africans. Clin. Exp. Hyp. 3(4): 861-70, 1981.

Gelfand, M. Shona Ritual, Juta and Co. Cape Town printed, 1-12, 1959.

Gelfand, M. Shona Religion with special reference to the MaKoreKore. Juta and Co. printed, 171-75, 1962.

Gelfand, M. Diet and Tradition in an Africnan culture, Eand S Livingstone published, 79-176, 1971.

Gelfand, M. The African Crucible. Rustica press. 139-163, 1967.

Gelfand, M. The Genuine Shona: Survival values of an African culture, Mambo press, 180-197, 1973.

Genest, J. Volume homeostasis and blood pressure. Ann. Intern. Med. 98(2): 744-49, 1983.

Goldin T. Estrogens excretory patterns in plasma levels in vegetarian and omnivorous women. New Engl. J. Med. 307: 1542-47, 1982.

Goto A., L. Tobian and J. Iwai. Potassium loading lowers hypereacive central nervous system in in Dahl S rats. Hypertension 3(supp 1):128-34, 1981.

Grim C.E, Luft F. C., Miller J., Meneeley G., Battarbee H., Hames C., and Dahl L. K. Racial differences in blood ptressure in Evans County, Georgia, sodium, potassium and plasma renin activity. J. Chronic Dis. 33: 87-94, 1980.

Grim, C.E. Genetic Studies in twins. J. Clin. Hypertens. 3: 74s-78s, 1987.

Grim, C.E. Renin and aldosterone in hypertensive blacks. J. Clin. Hyp. 3: 43s-46s, 1987.

Grim, C.E. Black survival, illness traced to genetic traits. Detroit Free Press 11A, January 21, 1988.

Guyton, A. and T. Coleman. A quantitative analysis of the pathophysiology of hypertension. Circulation Res. 24: 1-26, 1969.

Haddy, F. Sodium potassium pump in low renin hypertension. Annals Intern. Med. 98(2): 781-4, 1983.

Haddy, F. Endogenous digitalis like-factor or factors. New. Engl. J. Med. 316(10): 621-3, 1987.

Haddy, F. Potassium effects on contraction of arterial smooth muscle mediated by sodium potassium ATPase. Fed. Proc. 42: 239-45, 1983.

Haddy, F. Dietary sodium and potassium in th genesis, therapy, and prevention of hypertension. J. Am. Coll. Nutr. 6(3): 261-70, 1987.

Hall, C.E. and O. Hall. Comparative effectiveness of glucose and sucrose in enhancement of hypersalimentation and salt hypertension. Proc. Soc. Exp. Biol. Med. 123: 370-4, 1966.

Hamilton, M., G. Pickering and F. Roberts. The etiology of essential hypertension: 2. Scores for arterial blood pressure adjusted for differences in age and sex. Clin. Sci. 13: 11, 1954.

Harburg E., J. Erfurt, L. Hausetein, C. Chape, W. Schull and M. Scork. Socioecologic stress, suppressed hostility, skin color, and black and white male blood pressure: Detroit. Pychosomatic Med. 35: 276-96, 1978.

Haupert, T.G., C. Corrilli and L. Cantley. Hypothalamic sodium transport inhibitor is a high affinity reversible inhibitotr of Na-K ATPase. Am. J. Physiol. 247: F919-24, 1984.

Henry, J.P. Stress, salt and hypertension. Soc. Sci. Med. 26: 293-302, 1988.

Hermsmmeyer. Vascular muscle membrane cation mechanisms and total perripheral resistance. Hypertension 10(supp 1): I 20-I 22, 1987.

Hill D. Plasma hormones and lipids in men at different risk for coronary heart disease. Am. J. Clin. Nutr. 33: 1010-18, 1980.

Hollister, S.A., I. Tanaka, T. Imada, J. Onrot, I Biaggioni, D. Robertson, and T. Inagami. Sodium loading and posture modulate human ANP plasma levels. Hypertension 8(supp II): II-106-II-111, 1986.

Holly J., F. Goodwin, S. Evans, M. Vandengurg and J. Lendingham. Reanalysis of data in two Lancet papers on the effect of sodium and potassium on blood pressure. Lancet 2: 1384-7, 1981.

Humphreys, M. and Shan-yan Lin. Peptide hormones and the regulation of sodium excretion. Hypertension 11: 397-410, 1988.

Hunt J. Sodium intake and hypertension: a cause for concern. Ann. Intern. Med. 98: 724-28, 1983.

Intersalt 1986 Cooperative research group. An international cooperative study on the relation of blood pressure to electrolyte excretion in populations 1. Design and Methods. J. of Hypertension 4: 781-87, 1986.

Intersalt 1986 cooperative research group. An international cooperative study on the relation of blood pressure to sodium and potassium excretion. Brit. Med. J. 297: 319-28, 1988.

Inagami, T., K. Mizuno, M. Nakamaru and K. Higashimori. Local generation and release of angiotensin II from peripheral vascular tissues. Hypertension 11: 223-29, 1988.

Iimura I., T. Kijima and K. Kikuchi. Studies on the blood pressure lowering effect of potassium in essential hypertension. Clin. Science 61: 77s-80s, 1981.

Jin, H., J. Chen, R. Yang and S. Oparil. Impaired release of ANP in sodium chloride loaded SHR. Hypertension 11: 739-44, 1988.

Jones, J.J., M. Gelfand, and E. Kanengoni. Renin activity in black hypertensive patients in Rhodesia. S Afr. Med. J. 48; 2223-5, 1974.

Kageyama Y., H. Suzuki, K. Arima and T. Saruta. Oral calcium treatment lowers blood pressure in renovascular hypertensive rats by decreasing renin angiotensin system. Hypertension 10:375-82, 1987.

Kaminer, B. and W.P. Lutz. Blood pressure in the Bushmen of the Kalahari. Circulation, 22: 287-95, 1960.

Katz L. and E. Lindner. The action of excess sodium, calcium, and potassium on the coronary vessels. Am. J. Physiol. 124: 155, 1938.

Kawasaki T., C. Delea, F. Bartter, and H. Smith. The effect of increasing sodium and decreasing sodium intakes on blood pressure and other related variables in human subjects with idiopathic hypertension. Am. J. Med. 64: 193-8, 1977.

Kesteloot H., D.X. Huang, Y. Li, J. Geboers and J. Joossens. The relationship between cations and blood pressure in the People's Republic of China. Hypertension 9: 654-9, 1987.

Khaw K. T. and E. Barret-Connor. The association between blood pressure, age, and dietary sodium and potassium: apopulation study. Circulation 77: 53-61, 1988.

Kirkendall, M.W., W.E. Connor, F. Abboud, S. Rastogi, T. Anderson and M. Fry. The effect of dietary sodium chloride on blood pressure, body fluids, electrolytes, renal function, and seerum lipids of normotensive men. J. Lab. Clin. Med. 87: 418-34, 1976.

Koepke, J., S. Jones and G. DiBona. Sodium responsiveness of central of central alpha-2 adrenergic receptors in SHR. Hypertension 11: 326-33, 1988.

Kotchen, J.M. and T.A. Kotchen. Geographic effect of on racial blood pressure differences in adolescents. J. Chronic Dis, 31: 581-86, 1978.

Langford F. Dietary potassium and hypertension: Epidemiological data. Annals of Intern. Med. 98(2): 770-72, 1983.

Langford F. Dietary sodium, potassium and calcium in black hypertensive subjects. J. Clin. Hypertens. 3: 36s-42s, 1987.

Laragh, J.H. Personal views on the mechanisms of hypertension. Chapter 39, Hypertension Physiopathology and Treatment., 2nd Ed., McGraw-Hill, New York, 1983.

Larsson B. Abdominal adipose tissue distribution, obesity and risk of cardiovascular disease and death; a 13 year follow up of participants in the study of men born in 1913. Bt. Med. J. 288:1401-4, 1984.

Larsson, B. The health consequences of moderate obesity. Int. J. Obesity. 5: 97-116, 1981.

Lawton, W., C. Sinkey and A. Fitz. Dietary salt produces abnormal renal vasoconstrictor responses to upright posture in borderline hypertensive subjects. Hypertension 11: 529-36, 1988.

Leary, P.W. and A.C. Asmal. Plasma renin levels in Zulu hypertensives. S. Afr. Med J. 49; 673, 1975.

Light, K.C., J P. Koepke et al. Psychological stress induces sodium and fluid retention in in men at high risk for hypertension. Science 220: 529-31, 1983.

Losse H., W. Zidek, Zumkley, F. Weel and H. Vetter. Intracellular Na+ as a genetic marker for essential hypertension. Clin. Exp. Hyp. 3(4): 627-40, 1981.

Lowenstein, F.W. Blood pressure in relation to age and sex in the tropics and subtropics. A review of the literature and an Investigation in 2 tribes of Brazil Indians. The Lancet 389-91, February 1961.

Luft, F., Rankin, Bloch, Weyman, Willis, Murray, Grim, and Weinberger. Cardiovascular and humoral responses to extremes of sodium intake in normotensive black and white men. Circulation 60(3): 697-705, 1979.

Luft F.C., Fineberg, Miller, Rankin, Weinberger. the effects of age, race, and heredity in glomerular filtration rate following volume expansion andcontraction in normal man. Am. J. ci. 279: 15-24, 1980.

Luft, F.C., J. Miller, S. Cohen, N. Fineberg and M. Weinberger. Heritable aspects of salt sensitivity. Am. J. Cardiol. 61: 1H-6H, 1988.

MacGregor G, S. Smith, N. Markandu, R. Banks, and G. Sagnella. Moderate potassium supplementation in essential hypertension. Lancet 2: 567-70, 1982.

MacGregor, G. Sodium is more important than calcium in essential hypertension. Hypertension 7: 628-37, 1985.

Maddocks, I. Possible absence of essential hypertension in two complete pacific Island populations. Lancet 396 -401, August 1961.

Master, A., L. Dublin and H Marks. The normal blood pressure range and its clinical implications. J.A.M.A. 143 (17): 1464-70, 1950.

M'Buyamba-Kabangu, J., P. Lijen, D. Groeesenneken, J. Staessen, W. Lissens, W. Goossens, R. Fagard, and A. Amery. Racial differences in intracellular and transmembrane fluxes of sodium and potassium in erythrocytes of normal male subjects. J. Hypertens. 2: 647-51, 1984.

McCarron D. A., C. Morris and C. Cole. Dietary calcium in human hypertension. Science 217: 267-70, 1982.

McCarron, D.A. Low serum ionised calcium in patients with essential hypertension. New Eng. J. Med. 226-8, July, 1982.

McCarron, D. Divalent cations, anions and blood pressure. Annals Intern. Med. 98(2): 800-5, 1983.

Meneeley and Ball. Experimental evidence of chronic sodium chloride toxicity and protecive effect of potassium chloride. Am. J. Med. 713-25, 1958.

Meyer, P., R. Garay. Ion transport systems in hypertension. In: Genest (ed.), Hypertension, 2nd Ed., 1982, 108-11.

Metuh, E. God and Man. In: The African Religion. Geoffrey Chapman, London published; 170-171, 1981.

Miall, W.E., E.H. Kass, J. Ling, and K.L. Stuart. Factors influencing arterial pressure in the general population in Jamaica. Br. Med. J. 492-506, August 1962.

Miller J, M. Weinberger and J. Christian. Blood pressure response to potassium supplementation in normotensive adults and children. Hypertension 10: 437-42, 1987.

Minuz, P.,G. Covi, F. Paluani, M. Degan, C. Lechi, M. Corsato and A. Lechi. Altered excretion of prostaglandins and thromboxane metabolites in pregnancy induced hypertension. Hypertension 11: 550-6, 1988.

Miyamori, I., M.Ikeda, T. Matsubara, S. Okamoto, H. Koshida, T. Morise, and R. Takeda. Human artial natriuretic peptide during escape from mineralcorticoid excess in man. Cli. Sci. 73: 431-36, 1987.

Moorehead and Biggs. 2 amino-2methyl propanol as the alkanalizing agent in an improved continuous flow o-cresophthalein complexone procedure for calcium in serum. Clin. Chem. 20: 1458-60, 1974.

Morgan, K., S. Foord, G. Spurlock, B. Charalambaous, C. Dieguez, M. Scanlon, and M. Afzal mir. Release of an active sodium transport inhibitor from rat hypothalamic cells in culture. Endocrinology 116: 1642-4, 1984.

Morris, M., M.Cain, A. Russell, J. Elliott and J. Chalmers. Direct radioimmunoassay of human ANP in various normal and pathophysiological states: Increase in renal and cardiac failure during exercise. Clin. and Exp. Hyp. Theory and Practice. A9: 703-18, 1987.

Moser, M., R. Morgan, M. Hale, S. Hoobler, R. Remington, J. Dodge, and A. Macaulay. Epidemiology of hypertension with particular refence to the Bahamas. Am. J. Cardiol. 727-33, December 1959.

Murphree, M. Christianity and the Shona. University of London, Athlone Press, 4-14, 1969.

Oliver, W. J., E.L. Cohen, and J.V. Neel. Blood pressure, sodium intake, and sodium related hormones in the Yanomamo Indians, "No-Salt" culture. Circulation 52: 146-51, 1975.

Oparil, S. Increasaed sympathetic nervous system activity in salt dependent hypertension. In: National Institutes of Health, USA-Poland Symposium, Cardiovascular Disease. Washington, D.C.: US Dept. of Health and Human Services, 41-47, 1986.

Oshima T, H. Matsuura, K. Matsumoto, K.Kido, and G. Kajiyama. Role of cellular calcium in salt sensitivity of patients with essential hypertension. Hypertension 11: 703-707, 1988.

Overbeck H. W. and D. W. J. Clark. Vasodilator response to potassium in genetic hypertension, and renal hypertension. J. Lab. Clin. Med. 86: 973-83, 1975.

Page, L., A. Dammon, and R. Mollering. Antecedents of of cardiovascular disease in six solomon islands societies. Circulation XLIX: 1132-46, 1974.

Page L. Epidemiology of hypertension, chapter 45, in Hypertension edited by J. Genest, Kuchel, Hamet and Cantin, Mcgraw-Hill, 2nd edn 1983.

Parry, H. Ethioipian Cardiovascular studies. III The casual blood pressure in the Ethiopian highlands of Addis Ababa. East Afr. Med. J. 46(5): May 1969.

Pekka P., A. Nissinen, E,. Vartiainen, R. Dougherty, M.Mutanen, J. Iacono, H. Korhonen, P. Pietinen, U. Leino, S. Moisio and J. Huttunen. Controlled randomized trial of the effect of dietary fat on blood pressure. The Lancet 1-3, January 1983.

Perera. Depressor effects of potassium deficiency diets in hypertensive man. J. Clin. Invest. 32: 633-6, 1953.

Prineas, R.J. and R. Gillum. United States epidemiology of hypertension in Blacks, In: Hall et al., (eds.) Hypertension in Blacks, Year Book Medical Publishers published, 17-36, 1985.

Poulter, N., K.T. Khaw, B. Hopwood, M. Mugambi, S. Peart, G. Rose and P. Sever. Blood pressure and its correlates in an African tribe in urban and rural environments. J. Epid. and Commun. Hlth 38: 181-86, 1984.

Rasmussen. Cellullar calcium metabolism. Ann. Intern. Med. 98: 808-816, 1983.

Rasmussen,P.Barrett, Y.Takuwa and W. Apfeldorf. Calcium in the regulation of aldosterone secretion and vascular smooth muscle contraction. Hypertension 10(supp 1): I-23-I-26, 1987.

Resnick L., J. Nicholson, J. Laragh. Calcium metabolism in essential hypertension: Relationship to altered renin system activity. Fed. Proc. 45: 2739-45, 1986.

Richards, M.A., G. Nicholls, E. Espiner, H. Ikram, E. Hamilton, E. Wells, A. Maslowski and T Yandle. Endogenous angiotensin-aldosterone pressure relationships during sodium restriction. Hypertension 7: 681-87, 1985.

Rikimaru, T., Y. Fujita, T. Okuda, N. Kajiwara, S. Miyatani, M. Alpers and H. Koishi. Response of sodium balance, blood pressure, and other variables to sodium loading in Papua New Guinea Highlanders. Am. J. Clin. Nutr. 47(3): 502-8, 1988.

Robertson, D. D.G. Shand,J. Hollifield, A. Nies, J. Frolich and J. Oates. Alterations of the sympathetic nervous system and renin in borderline Hypertension. Hypertension 1: 118-24, 1979.

Rocella, E. J. A. Bowler, and M. Horan. Epidemiological considerations in defining hypertension. Med. Clin. North Am. 71(5): 795-801, 1987.

Saunders, G.M. and H. Bancroft. Blood pressure studies of negro and white men and women living in the Virgin Islands of the United States of America. Am. Heart J. 410-23, 1941.

Saville, A.M., P.Geer,B.Wang, R. Leadley and K. Goertz. A high salt meal produces natriuresis without elevating plasma atriopeptin. Proc. Soc. Exp. Biol. Med. 188: 387-93, 1988.

Seedat, Y.K., M.A. Seedat, and D.B.T. Hackland. Prevalence of hypertension in the urban and rural Zulu. J. Epid. Commun. Hlth. 36: 256-61, 1982.