

CHAPTER II HYPERTENSION

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INTRODUCTION

Hypertension (high blood pressure), when sustained over years expresses serious disabling consequences such as stroke, heart failure, ischaemic heart disease (IHD) and renal failure. In all, these complications must cost South Africa many millions of rand every year. Yet hypertension is now recognised to be a disease of lifestyle, in part the consequence of dietary indiscretions (excess calories and salt), obesity and lack of exercise. These are measures that require a population-based strategy for control. Yet there are those with hypertension who appear to suffer from none of these adverse lifestyle factors, and in whom there is a strong familial tendency. Clearly therefore the basis for research in South Africa should be to clarify which aspects should be tackled as part of a public health policy, and which aspects require intense laboratory research for further clarification of this important problem. This chapter will first examine the background to the problem, outline the mechanisms in hypertension, consider the role of ethnic factors, and briefly describe the principles of existing therapy. The problems of special population groups (e.g. the elderly) will then be further examined. Thereafter proposals for specific community-related research as well as for laboratory based progress will be made.

What is hypertension?

Hypertension is a disease in which a chronically elevated blood pressure, above normal limits, promotes end-organ damage such as stroke, CAD, heart failure and renal failure. Because each of these end-points is an amalgam of various factors that promote the disease in question ('risk factors') it is clear that absolute cut-off levels for the diagnosis of hypertension can be misleading. For example, in the South African black population where the blood cholesterol level (a major risk factor for IHD) is known to be low, hypertension seldom results in IHD. On the other hand, in white, Asian and 'coloured' South Africans, in whom blood cholesterol levels are on the whole much higher, hypertension much more frequently is associated with IHD. In fact, judging from data in Western Europe, coronary disease may be the major cause of mortality in such hypertensive populations. Therefore, a simple cut-off value of blood pressure (BP) elevation (above which hypertension is diagnosed and below which normality is diagnosed), can be misleading. The analogy would be setting a safe speed limit for car accidents. In fact the 'safe speed' varies with the location of the road, the visibility, the time of the day, the condition of the car, the mental clarity of the driver and the behaviour of other drivers. Nevertheless it remains true that in general a lower speed limit is on the whole associated with a lower incidence of fatal accidents. Thus in a similar way a low BP is, in general, associated with greater longevity and fewer end-organ complications.

To achieve a practical approach to the diagnosis of hypertension, for our South African population as a whole, a 'cut-off' diastolic BP value of 100 mmHg may be appropriate for the diagnosis of hypertension sufficiently severe to consider drug treatment,¹ while values between 90 and 100 mmHg are appropriate for the diagnosis of borderline hypertension. In this BP range, the presence of additional risk factors for cardiovascular disease such as smoking, hypercholesterolaemia, age, lack of physical exercise and diabetes mellitus, may mandate the additional of drug to non-drug therapy. In elderly patients vascular disease causes the systolic pressure to rise and the diastolic

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value to fall, so that the diagnosis of hypertension should be based on an increased systolic BP value above 160 mmHg, irrespective of the diastolic value. In every case it should be noted that for a given patient the BP may be highly variable and that the stress of seeing a doctor and visiting a hospital can falsely elevate the BP ('white coat hypertension'). Repetitive BP values in resting conditions are required before any firm diagnosis of sustained hypertension can be made.

The Consensus document of the Southern African Hypertension Society and the Heart Foundation allows a more sophisticated approach to the diagnoses of hypertension, which is defined as a consistently elevated systolic BP of 160 mmHg or more and/or a consistently elevated diastolic BP of 95 mmHg or more; from these values downwards to 140/90 mmHg defines borderline hypertension requiring, on the whole non-pharmacological (lifestyle modification) therapy.

How does hypertension arise?

The genesis of hypertension is complex and cannot readily be simplified. Nonetheless, it appears that at least five major models have evolved, each emphasising a different aspect of the hypertension process. In any given patient one of these factors may be more important than others, but often hypertension is multifactorial. Some of the factors emphasised include:

Excess adrenergic activity

It is often thought that emotional stress causes sustained hypertension. Because: $BP = \text{heart rate} \times \text{peripheral vascular resistance (PVR)}$ and because adrenergic activity through beta-receptor stimulation increases the heart rate and through alpha-receptor stimulation increases the peripheral arteriolar constriction and thereby the PVR, it is easy to see that excess adrenergic activity as an emotional stress could elevate the BP on a temporary basis. Nonetheless proof of this simple supposition has not been easy to establish. In physiological circumstances, besides the alpha-adrenergic mediated increase in arteriolar tone (and in PVR), there is also a simultaneous adrenergic stimulation of the beta₂ receptors that results in vasodilation. Thus adrenergic stimulation has two potentially conflicting effects. In a famous experiment carried out in 1959² a normal medical student was subjected to great emotional stress which caused a vigorous tachycardia and a marked increase (not decrease) in forearm muscular blood flow, whereas the BP increase was only modest (Fig. 1). In other words, for this adrenergic theory to be valid there should be something in addition to episodic stress that causes the BP to rise in a sustained rather than an intermittent fashion.

One modern concept is that repetitive small surges of BP damage the inner lining of the arterioles (vascular endothelium). The damaged endothelium releases a vasoconstrictive polypeptide called endothelin which causes a substantial degree of arteriolar constriction with, eventually, a sustained BP rise and leakage of protein into the urine i.e. micro-albuminuria.³ The increased pressure inside the arterioles causes more endothelial damage so that there is a vicious circle in operation (Fig. 2).

Supporting this hypothesis of an early increase in adrenergic activity, are the data of Lund-Johansen,⁴ who showed that in young hypertensives the haemodynamics are on the whole characterised by an increased heart rate and elevated cardiac output, compatible with the concept of overactivity of adrenergic beta-receptors. In contrast, older hypertensives have no such changes but rather an increase in the PVR, compatible with the proposal of endothelial damage. Arguing against this model is the finding that beta-blocker therapy is approximately equally effective in younger as in older white males.⁵ Yet the patients studied by Lund-Johansen were really young, in their early twenties, whereas the 'younger' patients in the Materson study had an average age of 50 years.

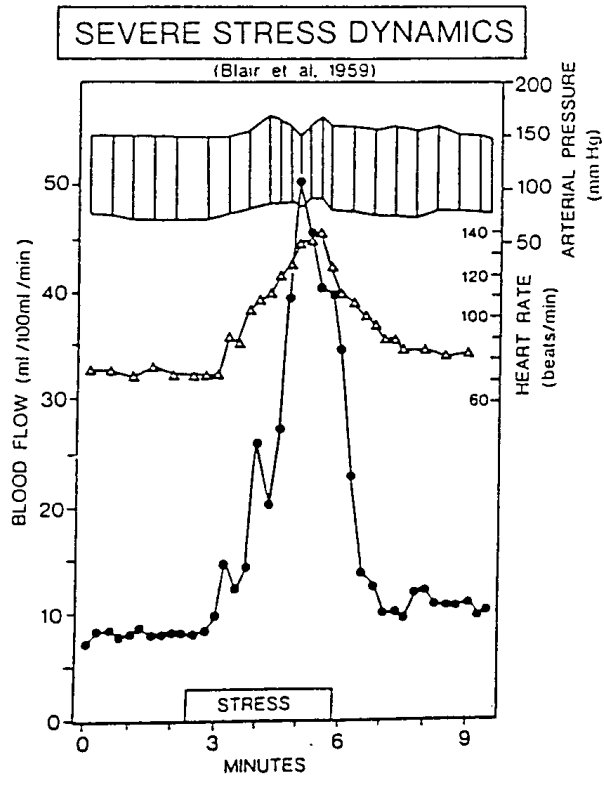


Figure 1. The effect of severe sudden emotional stress on a young medical student. Note the marked increase in heart rate, almost doubling, the vast increase in forearm blood flow (black dots) and the only modest increase in blood pressure. It is argued that emotional crises, of their own, are unlikely to cause sustained hypertension.²

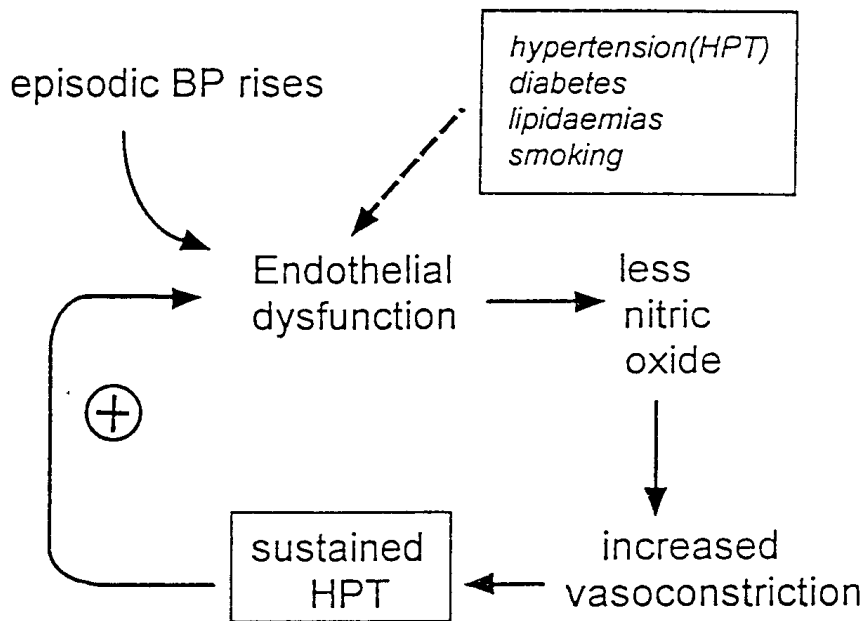


Figure 2. Mechanisms whereby episodic stress could give rise to sustained hypertension (Fig. copyright LH Opie).

The salt model

As far back as 1920 Allen,⁶ linked low salt restriction with the treatment of hypertension. The logic was that hypertension was known to be associated with renal disease and renal disease in turn caused sodium retention. Next the introduction of diuretic therapy in the early 1950s emphasised the possible role of sodium. It was noted that an antihypertensive effect could be obtained with low-dose diuretic which, apparently, did not cause any major increase in urine volume.⁷ It is now known that in approximately half of patients with hypertension, a high sodium intake can exaggerate the blood pressure level. Conversely, diuretic therapy is effective, depending on the dose given, again in approximately half or slightly more of the patients.⁵ Of interest though is that approximately half of the diuretic effect could in turn be ascribed to placebo.⁵

In terms of modern renal physiology, the concept could be as follows. In normal subjects a high sodium diet leads to an increased blood volume which inhibits the release of renin, with therefore less production of angiotensin II and less vasoconstriction of the efferent renal arteriole. Therefore, a high salt diet causes the blood flow through the glomerulus to increase with a greater sodium diuresis. Less angiotensin II also leads to a lower level of aldosterone secretion, which promotes a sodium diuresis because there is decreased sodium reabsorption in the distal tubule (Fig. 3).⁸ In certain *salt-sensitive hypertensive patients*, the above sequence does not hold. There is no increase in renal blood flow and no sodium diuresis in response to the high salt diet. These patients reacting adversely to the high salt intake are called non-modulators (Fig. 3).⁸

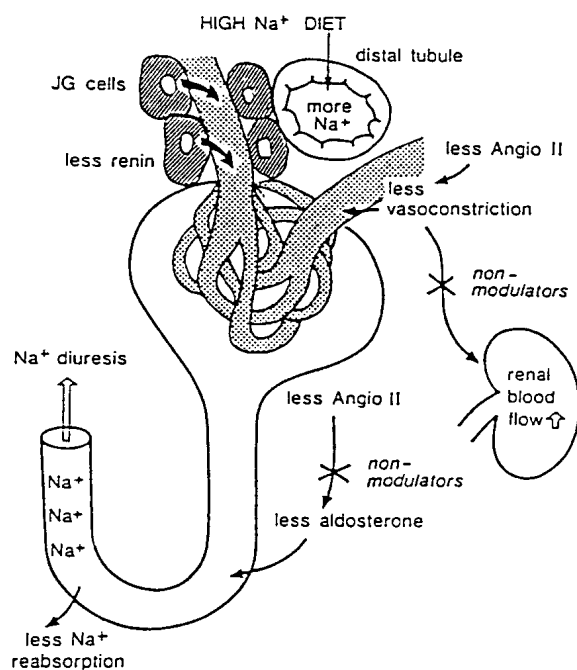


Figure 3. The concept of non-modulating hypertension - the normal reaction to an increased salt intake is absent (Fig. copyright LH Opie). For details see Hollenberg & Williams.⁸

Regardless of the exact processes involved, it is clear that certain salt-sensitive individuals are more susceptible than others to a high dietary salt intake and are more likely to develop hypertension as a result of excess salt in the diet. What is also clear is that salt-sensitivity and low renin-status are more frequent in black patients than in whites, at least in the USA.⁹

The renal model

Closely allied to the salt model, the renal model has an extensive historical pedigree. In 1898 Tigerstedt and Bergman¹⁰ discovered that a renal extract, when injected into dogs, put up the BP. The active substance in the renal extract was called renin. Much later, round about 1940¹¹ it became evident that renin was exerting its effect in increasing the BP by producing a substance which constricted the peripheral arterioles, eventually to be called angiotensin. To be more precise, renin converted inactive angiotensin I to active angiotensin II. Angiotensin II not only constricts arterioles but increases the secretion of aldosterone, a sodium-retaining hormone, from the adrenal cortex.

Originally it was thought that it would be relatively simple to classify each patient with hypertension into a high or low renin status and that those with high renin levels would automatically respond to a different type of therapy from the others. As pointed out in the preceding section, the sodium intake has a radically important role in influencing the rate of renin release. To assign a low renin status to a patient requires measurement not only of the renin level in the blood but of the simultaneous sodium intake as judged by the urinary sodium concentration.¹²

In South Africa there is particular interest in the proposal that black hypertensives have, on the whole, a low renin status.^{13,14,9} That means that in relation to the sodium intake, the blood renin level is low and, therefore, the mechanisms of adaptation to a high sodium intake are not as brisk as in other patients. The preexisting low renin status of such black hypertensives means that there cannot be much secretion in response to a high salt intake, so that a high salt diet would be more likely to result in sodium overload and hypotension.

Interaction of salt and renal models: In the USA it is known that black hypertensives, besides being salt-sensitive are also more prone to renal failure. When black hypertensives were salt-loaded, renal blood flow fell rather than rising as it should.¹⁵ The calcium antagonist nifedipine reverted the adverse renal haemodynamic changes.

Cell membrane pumps

On the basis of work done both in Johannesburg and in Cape Town, there is evidence for defective or impaired activity of the sodium pump on the cell membranes of hypertensive patients. While the Cape Town group¹⁶ studied a relatively small number of patients, both black and white and normotensives and hypertensives, the Johannesburg group¹⁷ studied a total of 154 subjects. Although there are a number of differences between these two studies in the results found, possibly explained by a poorer nutritional status of the black subjects in Johannesburg, the common finding is impaired activity of the sodium pump ($\text{Na}^+\text{-K}^+\text{/ATPase}$) in black subjects in both the Cape Town and the Johannesburg groups. If there is impaired capacity to eject sodium from cells in black hypertensive subjects, then sodium will accumulate within the cells, including those of the blood vessels. Then the sodium-calcium exchange mechanism would lead to increased internal calcium with an increased tendency to vasoconstriction (Fig. 4) and increased PVR. Because the activity of the sodium pump ($\text{Na}^+\text{-K}^+\text{/ATPase}$) is especially important in regulating the reaction to the sodium retention found in salt-sensitive hypertensive subjects, the proposed defect in this pump in black patients is especially serious (Fig. 5). Indeed, the finding that hypertension in black subjects is often salt-sensitive and appears to respond to vasodilator therapy by calcium antagonists, but poorly to the ACE-inhibitors, supports this line of reasoning. Likewise the poor response to beta-blockade as monotherapy could be in part explained by a similar mechanism, because beta-blockade works in part through its inhibitory effect on renin secretion. In contrast, during diuretic co-therapy when there is stimulation of the renin-angiotensin system, the better response to ACE-inhibition and beta-blockade can also be explained.

The metabolic model: insulin resistance.

Recently there has been a great deal of emphasis on the concept that hypertension does not occur on its own but is often associated with obesity and diabetes mellitus (Fig. 6). Even in non-obese

hypertensives, some of the abnormalities found in obesity and in obese diabetics, such as insulin resistance, have been traced.¹⁸ According to this view, hypertension is part of a generalised metabolic abnormality in which insulin resistance plays a prominent part. Lack of exercise seems to predispose to this mechanism.¹⁹ That means that for any given intake of carbohydrate, the blood insulin level rises higher than it should. It is not exactly clear why an increased insulin level should promote hypertension,²⁰ and indeed many of the animal data are conflicting. Nonetheless there

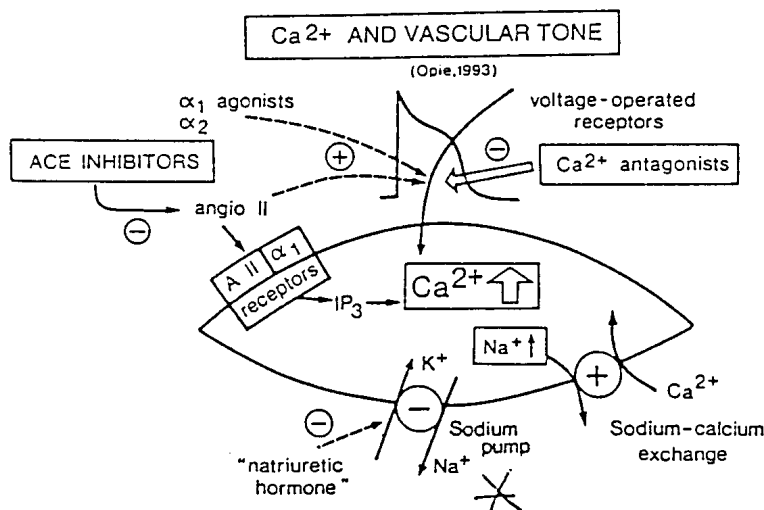


Figure 4. The role of the sodium pump in regulating internal sodium and therefore internal calcium in vascular smooth muscle (Fig. copyright LH Opie).

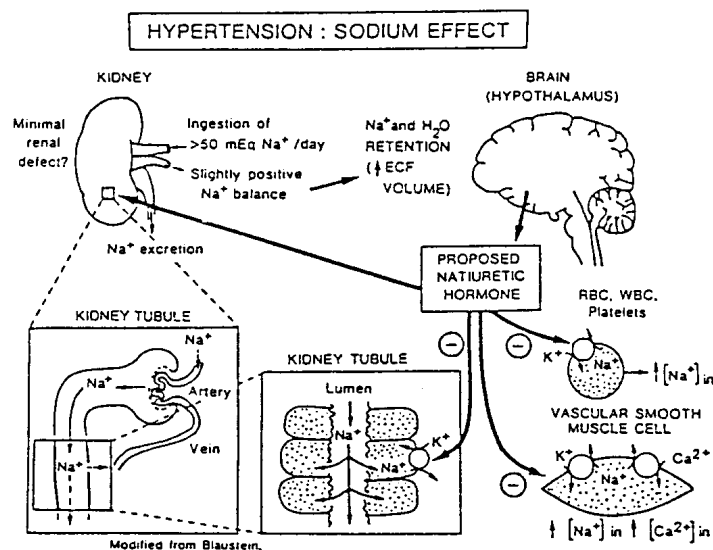


Figure 5. Proposals to link a high sodium diet to increase vascular smooth muscle tone. A slightly positive sodium balance causes sodium and water retention, which elicits the release of the proposed natriuretic hormone which inhibits sodium reabsorption in the renal tubule, thereby compensating for the positive sodium balance, while intracellular sodium rises as the Na^+/K^+ exchange is inhibited. The rise of cell Na^+ followed by an increase of Ca^{2+} as a result of $\text{Na}^+/\text{Ca}^{2+}$ exchange. Modified.⁴⁶

appear to be sufficient mechanisms for such a hypertensive effect of insulin to be regarded as probable. A common proposal is that insulin may increase adrenergic activity and/or cause sodium retention. Other workers²¹ stressed the possible role of obesity itself in impairing renal reabsorption of sodium, possibly acting through a physical mechanism such as the pressure of the obese tissue on the kidneys. Whatever the mechanism, it is clear that hypertension and obesity as well as that type of diabetes associated with obesity (type II non-insulin dependent diabetes) are all intimately linked. Thus to make an impression on the incidence of hypertension in the population *requires active lifestyle modification to lessen the incidence of obesity*. Thereby, also, as a major additional bonus the incidence of obese dependent diabetes should be reduced.

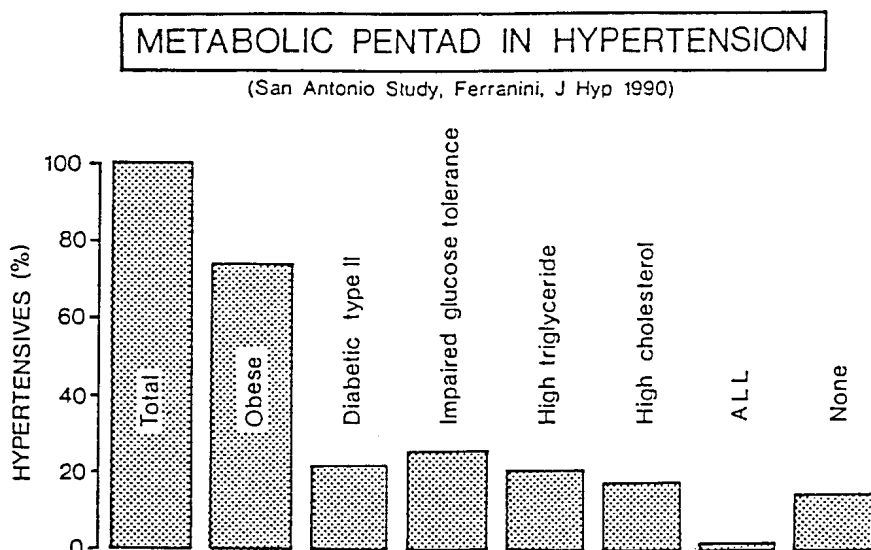


Figure 6. The metabolic pentad thought to exist in hypertension is composed of obesity, type II diabetes, impaired glucose tolerance, high blood triglyceride levels, and high blood cholesterol levels. Of these, obesity is by far the most common. Data from Ferrannini, 1990.

Regarding the metabolic theory for hypertension, there is now a great deal of emphasis on the concept that early fetal or neonatal nutrition may predispose to later onset of adult diabetes.²² A low birth-weight may cause damage to the pancreas and in later life, overeating, particularly of sugar and similar carbohydrates, may then precipitate adult diabetes because of the pre-existing weakness of the pancreas.

Theories for hypertension in black South Africans

From these various proposed mechanisms, of considerable interest are the suggestions that in South African black hypertensive patients, there may be:

1. A genetic (or possibly acquired) defect in the sodium pumping mechanism, making these subjects more susceptible to a high salt intake.
2. Also in these subjects, there may be a relatively inhibited renin-angiotensin system, thereby increasing the salt-sensitivity and decreasing the benefit to be obtained from certain antihypertensive agents such as the ACE-inhibitors.

3. Nutritional defects early in life might have late effects in precipitating diabetes, a disease often associated with obesity and hypertension.
4. Obesity, hypertension and non-insulin-dependent diabetes may be linked through the common denominator of insulin resistance. Although not well studied in black South Africans, it is a common clinical observation that these three conditions frequently coexist.

How prevalent is hypertension in South African communities?

In general, it is often thought that about one-fifth of most population groups throughout the world have hypertension, depending of course on the criteria used to define hypertension. Of these hypertensives, many are in the elderly population group when the BP so often increases that the majority of elderly subjects have hypertension according to current criteria. The best population studies in South Africa have been carried out in Zulus and Indians,¹⁴ in the Cape 'coloured' population²³ and on three white rural communities in the Cape, the latter being the CORIS study.²⁴ In general, these studies show that the Indian population has the lowest incidence of hypertension (about 14%), next comes the white community with an intermediate value (17-18%) while the urbanised Zulus have a higher incidence (25%). The latter high value is not caused by any inherent ethnic differences, because in rural Zulus, the incidence of hypertension is between 2% and 8%.²⁵ Likewise other non-urban black communities in Africa have a low incidence of hypertension.²⁶ It would naturally be important to try to confirm the South African rural figures in other rural communities, and in current rural conditions that might well have changed since 1981.

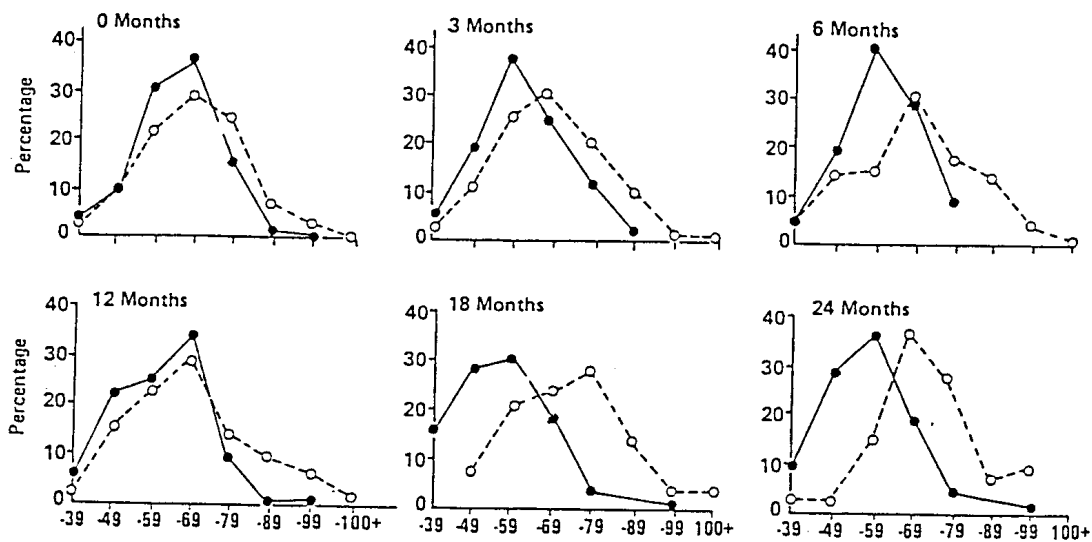
Effect of urbanisation

It follows that the process of urbanisation of blacks in this country may considerably increase the risk of hypertension. This is not unique to South Africa and similar trends have been observed in Kenya²⁷ in Tanzania²⁶ and in Zimbabwe.²⁸ The Kenyan study is especially excellent in that subjects were followed from the time of urbanisation onwards (Fig. 7). The mechanisms probably involved an increased dietary salt intake, a decreased potassium intake and weight gain as well as increased 'stress'. In the Intersalt study,²⁹ Kenyans with a low salt intake had a low blood pressure, but whether these Kenyans were urbanised or not is unknown. It should be noted that urbanisation and immigration from a rural to an urban environment could be an extremely stressful life event. Objectively there is a modest increase in pulse rate especially in males, reflecting increasing adrenergic discharge. Such psychological stress may potentiate the hypertensive effect of sodium loading, and of other adverse effects as weight gain.

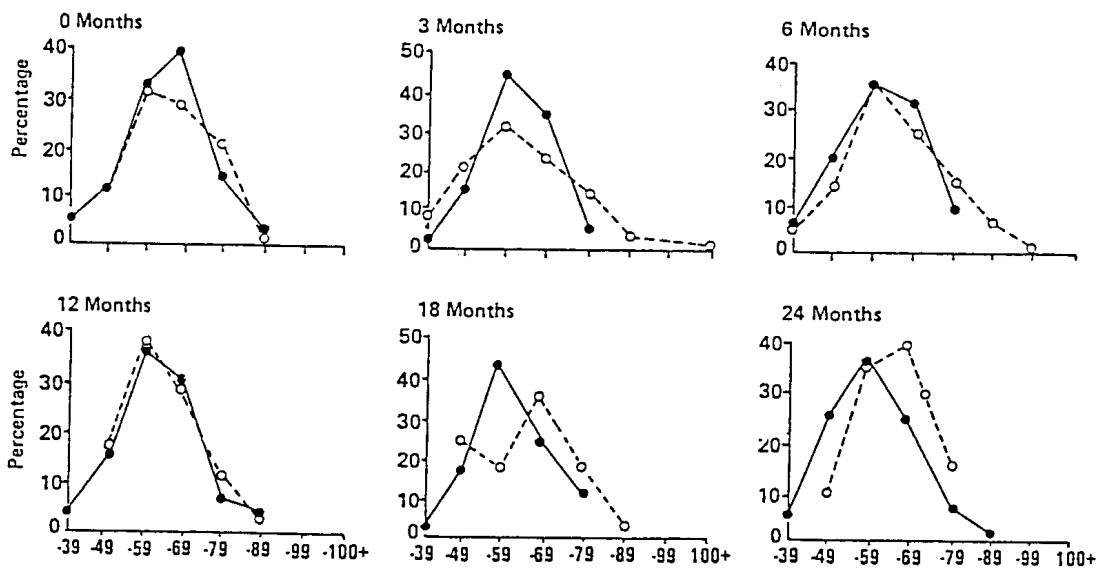
The implications for the South African Health Policy are two-fold. First, any intense campaign to detect and treat hypertension should not be directed towards rural blacks but rather towards those who are urbanised or about to undergo urbanisation. Second, there should be definite environmental factors involved in the process of urbanisation which could be analysed, defined and prevented.

How effective is existing therapy?

Many antihypertensive drugs are currently available. It is almost a truism that no patient with hypertension who is correctly treated fails to respond by a reduction in BP. As an exception, there is a small number of patients with hypertension secondary to other causes such as severe renal disease in whom reduction of the BP becomes extremely difficult. Therefore, from the South African point of view no specific research is required for the treatment of hypertension. Rather, the question becomes, which drugs are sufficiently cheap to use in significant amounts? It is apparent that three of the major categories of antihypertensive drugs, namely the diuretics, the adrenergic modifiers and the vasodilators, are each represented by at least one drug that is outstandingly cheap (hydrochlorothiazide, reserpine, and hydralazine). Therefore, again, the problem lies less in the availability or cost of drugs than in getting the hypertension diagnosed, the patient treated and in ensuring compliance of the patient with the therapy.



Males



Females

● = Controls ○ = Urbanised Kenyans

Figure 7. Effect of urbanisation on diastolic blood pressure. Note that even on arrival in the city (0 months) the BP increases somewhat, especially in males.²⁷

What research should be undertaken in the community?

It has already been argued that:

1. Hypertension may have a different causation in black subjects, involving increased sodium sensitivity and defects of membrane sodium pumping.
2. Black subjects tend to have low plasma renin values.
3. Black subjects when subjected to urbanisation undergo an increased risk of hypertension with an incidence at least twice as high as that of the rural blacks. Whereas the changes in membrane sodium pump activity and in plasma renin level may (but are not definitely) be related to genetic factors, it is clear that urbanisation is an environmental factor.

Urbanisation

If hypertension is a potentially lethal disease, as it is, and if the incidence of hypertension is more than doubled during the process of urbanisation, then clearly much more should be known about the factors involved. Although urbanisation has been relatively well studied in Kenyan and Zimbabwean blacks, there are few studies in South Africa. If genetic factors make the black population more susceptible to a high sodium intake (salt sensitive hypertension), then an increased salt intake during urbanisation could be one important factor in precipitating hypertension. This factor would be of special importance if coupled with a decreased potassium intake, because in ways not clear, potassium seems to protect from sodium effects.²⁹ Some of the major factors that need to be documented during the process of urbanisation are:

- (a) dietary salt and potassium intake;²⁷
- (b) total calorie intake and content of simple carbohydrates;
- (c) weight;²⁷
- (d) an index of insulin resistance (if possible fasting glucose and insulin levels and even better values after a glucose load);
- (e) smoking, and its possible effect in conjunction with increased salt loading;
- (f) alcohol; and
- (g) psychosocial stress³ - using a simple measure such as the heart rate.

Specific research proposals are as follows: Ideally a group of black subjects should be selected and studied *before and after urbanisation*. Furthermore, urbanisation might involve the process of relocation of the whole family from a rural to an urban environment, or only the subject might relocate, leaving the family behind. There are as yet no detailed studies on the difference between these two processes. It would seem that the usual process of transfer of a black worker from his rural environment to a mining compound or to an urban 'hostel' would involve more than one factor - that is to say not only would the subject be urbanised but he would also be removed from normal family influences. To cover this possibility a further research study should be undertaken to compare the BP increase in subjects undergoing 'solitary' versus 'family' urbanisation.

The elderly hypertensives

There is an increasing number of elderly subjects in our population, with the major increase at present being in the white group. Future increases can be anticipated in the black population, and indeed the largest percentage increase of any group will be in elderly black females. As the majority of elderly patients are, by current criteria, hypertensive, at least when dealing with white subjects,³¹ it is apparent that the prevention and management of hypertension in this group is of utmost importance for community health. The major purpose of active treatment of elderly patients is to avoid the development of stroke, which greatly impairs the physical activity of any elderly patient, and also greatly increases the cost of maintaining such an elderly person alive. As in younger patients, lifestyle management such as sodium restriction and increased physical activity will often reduce the BP. In other patients, administration of a simple and cheap diuretic will work with, at the most, one further added agent.

Research requirements are as follows: Much more must be known about hypertension in elderly blacks in this country. Studies already in progress in Bloemfontein will establish the incidence of hypertension in this group. Next the seriousness and possible complications of hypertension in elderly blacks need definition by a population survey. Then there should be a longitudinal study

(possibly under-way in Bloemfontein) in which groups of patients admitted to old-age homes or to 'retirement villages' or to rural environments where they can be followed up, are monitored progressively over the years. The parameters that should ideally be monitored include salt intake, physical activity, and insulin sensitivity.³² There should be an 'intervention group' which includes lifestyle modification and (possibly) diuretic treatment, to compare with a non-intervention group. Because it is supposed that hypertension becomes the norm in the elderly population, it would be ethically acceptable to start with a group of patients aged say 60 or 65 or even 70 years and to follow them up on the assumption that the majority would develop hypertension. It should also be possible to test lifestyle factors that could result in such hypertension. Possibilities as in the younger age groups are a high salt intake, weight gain, lack of exercise, and insulin resistance.

Obesity

As already emphasised, obesity seems to be linked to hypertension by insulin resistance, which may explain why obesity predisposes to CAD in white women.³³ In addition, obesity is a direct risk factor for left ventricular hypertrophy, even apart from the association with hypertension³⁴ Left ventricular hypertrophy, that is to say an enlarged and thickened left ventricle of the heart, has adverse effects on cardiovascular prognosis.³⁵ Management of obesity starts with prevention which, in turn, starts with cultural values that emphasise thinness. Values in urbanised blacks will change with time, and they too will swing to the other extreme and become subject to the abnormal pressure exerted on white urban females to be excessively thin. In the meantime, management of obesity in a middle-aged female who has been obese all her life is not easy.

The research proposals are as follows: A first important question requiring epidemiological study is whether obesity in adult black females is really associated with hypertension. Excellent studies already exist for the Cape coloured population.^{23,36} Next is to devise practical means of either treating or avoiding obesity in middle-aged females. Since obesity is also a risk factor for several other diseases besides diabetes and heart disease, and including osteo-arthritis, the total cost of obesity to the country is large. We need to know whether simple advice to reduce weight ever works, whether the addition of weight-reducing drugs such as dexfenfluramine is required, and whether aerobic exercise gives benefit. From the long term point of view, it may be needed to inculcate new values at the level of high school education with the ultimate aim of general weight loss in the urbanised population.

Severe or urgent hypertension

While this document largely concentrates on those many hypertensives who have mild-to-moderate disease, it should not be forgotten that there is a minority with severe hypertension, with threat of stroke, heart failure, or renal failure, who may require intense and careful investigation and follow-up at an academic teaching hospital. These patients are not suited for management in the community. Ideally there should therefore be rapid referral lines which can flow from the peri-urban community clinics through to neighbouring secondary and tertiary hospitals.

The research proposal is to work out how to manage apparently severe hypertension in the community, to deal with times when the aid of a secondary or tertiary hospital cannot be invoked. For example, could a nurse in fact be taught to distinguish between:

- (i) patients with severe hypertension but not really acutely ill; and
- (ii) those with threatened end-organ damage such as heart failure or encephalopathy, who would need hospital care? Would it be possible for her to manage these patients in local circumstances by conventional oral antihypertensive therapy, rather than risking the delays of referral? While there are several plans for the management of hypertension in the community at lower levels, some plan of action needs to be worked out for these high BP levels.

Comparison between South African and American blacks

An important question is not only why hypertension is more common in urbanised blacks, but whether at a given level of BP elevation, the resultant disease is more serious in black subjects. This proposal has often been made in relation to black hypertensives in the USA. There has been a fierce debate about whether the underlying cause is environmental or genetic.³⁷ In American blacks there are abnormalities in the diurnal BP pattern when day values are compared with night values, using the technique of ambulatory BP monitoring.³⁸ The most important finding is that the expected nocturnal fall in BP is less than it should be in black subjects. The result is a greater 24 hour 'blood pressure load' in blacks for any given clinic BP.³⁸ In contrast, South African blacks appear to have normal diurnal BP variations, similar to those of South African whites and different from American blacks.³⁹ This study is of considerable importance, particularly in that authors were able to compare South African with American blacks.

Research proposals. In view of the extensive documentation of the effects of hypertension in American blacks, it is important to clarify which aspects would overlap between the South African and American groups and which aspects would differ. For example, are South African blacks as a group salt-sensitive? There are, as far as can be ascertained, no studies on the effects of salt loading in South African blacks, and such studies need to be undertaken. Is the pressor response to cold different in South African and in American blacks?⁴⁰ Further comparative studies between these two population groups are required, with white South Africans as a control group. Outstanding questions are:

- (i) the degree of salt sensitivity in each population group;
- (ii) the urine sodium/potassium ratio;
- (iii) the red cell sodium transport capacity;
- (iv) the sensitivity of peripheral vasoconstrictory mechanisms (cold pressor test).

Left ventricular hypertrophy (LVH)

This condition is common in hypertensives and, it is thought, especially in black hypertensives, is largely related to the degree of BP elevation. Yet there is evidence, albeit imperfect, that a high salt intake may predispose to LVH⁴¹ and that salt restriction may aid in regression of LVH.⁴² From the research point of view, it would therefore be important to assess the possible development of LVH in the monitored group of black migrants undergoing urbanisation. The current gold standard of LVH is echocardiography. Therefore this study could be undertaken where the appropriate specialised facilities exist near to groups of new migrants undergoing urbanisation - for example, at the Department of Cardiology, Baragwanath Hospital.

What further laboratory research is required?

The most pressing issue is to establish whether or not there is a genetic defect involved in the impaired capacity of cells from black hypertensive patients for the outward pumping of sodium. It is important to understand whether this is a genetic or an environmental defect because, if genetic, then vigorous public health policy would be required to control sodium intake specifically in the black population. Genetic techniques can vary from those which are relatively complex and involve molecular biology to those which are relatively simple,⁴³ but such a study should be undertaken in consultation with genetic experts. This study could have enormous practical importance because, if genetic, then salt limitation should be the norm for South African blacks.

Furthermore, the sodium pump activity of isolated red cells should be followed up during the process of urbanisation. If urbanisation doubles the incidence of hypertension in black subjects, and if the

sodium pump activity is important, then defects in the activity of this pump may become apparent during the process of urbanisation.

There should also be more studies on elderly hypertensives using animal models if needed. The reason is that very little is known about the mechanism for the increased tendency to hypertension in the elderly. It is usually assumed that thickened arteries (arteriosclerosis) are responsible but, equally, other mechanisms could be involved, such as, for example, reduced release of atrial natriuretic peptide as proposed in a rat model by Opie.⁴⁴ We also need information about sodium pump activity and insulin resistance in ageing subjects.

Reservations: Socio-economic factors.

It would be clear that the process of urbanisation in this country is often accompanied by severe poverty and urgent need for food and survival. Lifestyle studies in such subjects are not relevant, nor is an increase in BP the most serious of the health hazards for such threatened individuals. Therefore, the process of urbanisation needs to be studied in relatively 'normal' black subjects, sufficiently wealthy not to be desperately struggling to survive, and such individuals could possibly best be found in the relatively settled communities of the Johannesburg or Durban areas.

Summary of Research Proposals

According to the existing information, there are two population groups of hypertensives in South Africa who are particularly prone to an increase of BP and therefore hypertension. These two groups are black subjects undergoing urbanisation, and elderly subjects. It is argued that much more needs to be known about the urbanisation process and, equally, much more needs to be known about elderly hypertensives, particularly blacks. Other population groups that need to be targeted and studied include obese patients, particularly obese diabetics, and those with severe or apparently urgent hypertension. A longitudinal study of subjects changing from the rural to the urban environment is the most crucial study which should be linked to an in-depth assessment of specific laboratory parameters such as measurement of sodium pump activity.

REFERENCES

1. Consensus Symposium. Management Guidelines in Hypertension in Southern Africa. *SAMJ* 1992;**82**(Suppl):1-4.
2. Blair DR, Glover WE, Greenfield ADM, Roddie IC. Excitation of cholinergic vasodilator nerves to human skeletal muscles during emotional stress. *J Physiol* 1959;**148**:633-647.
3. Pedrinelli R, Giampietro O, Carmassi F *et al.* Microalbuminuria and endothelial dysfunction in essential hypertension. *Lancet* 1994;**344**:14-18.
4. Lund-Johansen P. Twenty-Year Follow-up Hemodynamics in essential hypertension during rest and exercise. *Hypertension* 1991;**Suppl III**:54-61.
5. Materson BJ, Reda DJ, Cushman WC *et al.* Single-drug therapy for hypertension in men. A comparison of six antihypertensive agents with placebo. *N Engl J Med* 1993;**326**:914-921.
6. Allen FM. Arterial Hypertension. *JAMA* 1920;**74**:652-655.

7. Cranston WI, Juel-Jensen BE, Semmence AM, *et al.* Effects of oral diuretics on raised arterial pressure. *Lancet* 1963;ii:966-969.
8. Hollenberg NK, Williams GH. *Abnormal renal function, sodium-volume homeostasis, and renin system behavior in normal-renin essential hypertension.* In: Laragh JH, Brenner BM, eds. *Hypertension: Pathophysiology, Diagnoses and Management.* New York: Raven Press, 1990:1349-1370.
9. Blaustein MP, Grim CE. *The pathogenesis of hypertension: Black-White differences.* In: Saunders E, ed. *Cardiovascular Diseases in Blacks.* Philadelphia: F A Davis Company, 1991:97-114.
10. Tigerstedt R, Bergman PG. Niere und Kreislauf. *Skandinavisches Archiv fur Physiologie* 1898;8:223-271.
11. Page IH, Helmer OM. A crystalline pressor substance (angiotonin) resulting from the reaction between renin and renin-activator. *J Exptl Med* 1940;71:29-42.
12. Case DB, Wallace JM, Keim HJ *et al.* Possible role of renin in hypertension as suggested by renin-sodium profiling and inhibition of converting enzyme. *N Engl J Med* 1977;296:641-646.
13. Hypertension in blacks and whites. Editorial. *Lancet* 1980;ii:.
14. Seedat YK. Race, Environment and Blood Pressure. The South African Experience. *J Hypertens* 1983;1:7-12.
15. Campese VM, Parise M, Karubian F, Bigazzi R. Abnormal renal hemodynamics in black salt-sensitive patients with hypertension. *Hypertension* 1991;18:805-812.
16. Worthington MG, Wendt MC, Opie LH. Sodium transport in hypertension: assessment of membrane-associated defects in South African black and white hypertensives. *J Human Hypertens* 1993;7:291-297.
17. Touyz RM, Milne FJ, Reinach SG. Racial differences in cell membrane ATPases and cellular cation content in urban South African Normotensive and hypertensive subjects. *Am J Hypertens* 1993;6:693-700.
18. Facchini F, Ida Chen YD, Clinkingbeard C *et al.* Insulin resistance, hyperinsulinemia, and dyslipidemia in nonobese individuals with a family history of hypertension. *Am J Hypertens* 1992;5:694-699.
19. Endre T, Mattiasson I, Hulthen L *et al.* Insulin resistance is coupled to low physical fitness in normotensive men with a family history of hypertension. *J Hypertens* 1994;12:81-88.
20. Morris AD, Petrie JR, Connell JMC. Insulin and hypertension. *J Hypertens* 1994;12:633-642.
21. Hall JE. Renal and cardiovascular mechanisms of hypertension in obesity. *Hypertension* 1994;23:381-394.
22. Hales CN. Fetal nutrition and adult diabetes. *Scientific American* 1994;1:54-63.
23. Steyn K, Jooste PL, Fourie JM *et al.* Hypertension in the coloured population of the Cape Peninsula. *SAMJ* 1986;69:165-169.
24. Steyn K, Rossouw JE, Jooste PL *et al.* The intervention effects of a community-based hypertension control programme in two rural South African towns: the CORIS study. *SAMJ* 1993;83:885-891.
25. Seedat YK, Hackland DBT, Mpointshane J. The prevalence of hypertension in rural Zululand. *SAMJ* 1981;60:7-10.
26. Mtabaji JP, Nara Y, Yamori Y. The cardiac study in Tanzania: salt intake in the causation and treatment of hypertension. *J Human Hypertens* 1990;4:80-91.
27. Poulter NR, Khaw KT, Hopwood BEC *et al.* The Kenyan Luo migration study: observations on the initiation of a rise in blood pressure. *BMJ* 1990;300:967-972.
28. Mufunda J, Somova L, Chifamba J. Pathophysiological mechanisms of urbanisation-related hypertension and the sodium pressor response in black Zimbabweans. *SAMJ* 1992;82:507-510.
29. Intersalt Cooperative Research Group. Intersalt: an international study of electrolyte excretion and blood pressure. Results for 24 hour urinary sodium and potassium excretion. *BMJ* 1988;297:319-328.
30. Seedat YK, Seedat MA, Hackland DBT. Biosocial factors and hypertension in urban and rural Zululand. *SAMJ* 1982;61:999-1002.
31. Working Group on Primary Prevention of Hypertension. Report of the National High Blood Pressure education Program Working Group on Primary Prevention of Hypertension. *Arch Intern Med* 1993;153:186-208.
32. Dengel DR, Pratley RE, Hagberg JM, Goldberg AP. Impaired insulin sensitivity and maximal responsiveness in older hypertensive men. *Hypertension* 1994;23:320-324.
33. Manson JE, Colditz GA, Meir BS *et al.* A prospective study of obesity and risk of coronary heart disease. *N Engl J Med* 1990;322:882-889.
34. De Simone G, Devereux RB, Roman MY *et al.* Relation of obesity and gender to left ventricular hypertrophy in normotensive and hypertensive adults. *Hypertension* 1994;23:600-606.
35. Macmahon SW, Wilcken DEL, MacDonald GJ. The effect of weight reduction on left ventricular mass. A randomized controlled trial in young, overweight hypertensive patients. *N Engl J Med* 1986;314:334-339.
36. Steyn K, Fourie J, Rossouw JE *et al.* Anthropometric profile of the coloured population of the Cape Peninsula. *SAMJ* 1990;78:68-72.
37. Murray RF. Skin color and blood pressure. Genetics or environment? *JAMA* 1991;265:639-640.
38. Gretler DD, Fumo MT, Nelson KS, Murphy MB. Ethnic differences in Circadian hemodynamic profile. *Am J Hypertens* 1994;7:7-14.
39. Fumo MT, Reeger S, Lang RM *et al.* Diurnal blood pressure variation and cardiac mass in American blacks and whites and South African blacks. *Am J Hypertens* 1992;5:111-116.
40. Calhoun DA, Mutinga ML, Collins AS, *et al.* Normotensive blacks have heightened sympathetic response to cold pressor test. *Hypertension* 1993;22:801-805.
41. Kupari M, Koskinen P, Virolaimen J. Correlates of left ventricular mass in a population sample aged 36 to 37 years. Focus on lifestyle and salt intake. *Circulation* 1994;89:1041-1050.
42. Beil AH, Schmieder RE, Messerli FH. Salt intake, blood pressure and cardiovascular structure. *Cardiovasc Drugs Ther* 1994;8:425-432.
43. Davidson JS, Opie LH, Keding B. Sodium-potassium co-transport activity as genetic marker in essential hypertension. *BMJ* 1982;284:539-541.
44. Opie LH, Owen P, du Toit EJ, Norton GC. Decreased rates of release of atrial natriuretic peptide from isolated hearts from aging hypertensive rats. *Am J Hypertens* 1992;5:748-753.
45. Blaustein MP. Sodium ions, calcium ions, blood pressure regulation and hypertension: a reassessment and a hypothesis. *Am J Physiol* 1977;232:C165-C173.
46. Ferrannini E, Haffner SM, Stern MP. Insulin sensitivity and hypertension. *J Hypertens* 1990;8(Suppl 7):S169-S173.