THE DEVELOPMENT OF A METHOD TO EVALUATE THE USE AND MEDICAL AND SOCIOECONOMIC IMPLICATIONS OF ANTIHYPERTENSIVE DRUG TREATMENT IN THE MAMRE COMMUNITY.

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ABREVIATIONS

ACE	Angiotensin-converting enzyme
ANS	Autonomic nervous system
ATC	Anatomical, Therapeutic and Chemical classification
CERSA	The Centre for Epidemiological Research in South Africa
D.S.	District sugeon
DUR	Drug Utilisation Review
HDL	High density lipoproteins
JNC	Joint National Committee
K^+	Potassium
LDL	Low density lipoproteins
mmHg	Millimetres of mercury
MRC	Medical Research Council
RSA	Republic of South Africa
WHO	World Health Organisation
UCT	The University of Cape Town
U.K.	United Kingdom
U.S.	United States
VLDL	Very low density lipoproteins

ABSTRACT

The overall aims of this research were to develop and evaluate a method for Drug Utilisation Review in a primary health care setting. More specifically, it was to evaluate the use of antihypertensive drugs and their medical and socioeconomic consequences in the Mamre community.

One hundred and ninety five residents, 35 years or older, known to be on antihypertensive treatment for more than three months, participated in the study. The data were collected in two phases. The first involved the administration of a questionnaire by trained interviewers and the second involved the review of the patients medical records. The questionnaire was divided into 3 sections:-

1. to obtain background information and particulars of the participants and the prescribers
2. to obtain information on all medicines taken by the participants and the type of medical facility they attended
3. to obtain information on the impact of antihypertensive drugs on the participants' social well being, their financial burden and the perceived side effects experienced as a result of these agents.

Analysis of the results showed that the average hypertensive patient in the Mamre community was female (73.8%), with a standard 5 or 6 education and was 59 years old. They usually had one or more of the following concomitant diseases; gout or rheumatic conditions, diabetes and heart problems. Approximately 70% of the participants attended state run medical facilities

(district surgeons, day hospitals and teaching hospitals). Nearly a quarter of the participants attended more than one medical facility.

A total of twenty-seven different drugs were taken by the study participants for their hypertension but 61.5% of them were receiving only one drug.

Approximately 70% of the participants were estimated to be compliant or probably compliant with their antihypertensive treatment. Eighty five percent of the participants perceived themselves to feel better on their treatment and 88% were satisfied with their medical care.

Approximately 24% of the study participants were in paid employment. While 40% of the participants were responsible for payment for their visit and medicines, 75% of these attended one of the state facilities. About half of the participants who had to pay for their treatment themselves could not afford to. The participants attending the state facilities either paid nothing or had to pay themselves. The mean cost of a doctors visit to a state facility was R3.00, while the mean cost of the medicines was R7.12. Participants who attended private doctors either paid for their own treatment or it was paid for by a third party (eg. medical aid, employer). The mean cost of a visit to a private doctor was R9.14 and the mean cost for medicines was R41.00.

The dose of the antihypertensive drugs were found to be correct 70% of the time. Thirty six percent of the participants stood a theoretical chance of experiencing a drug interaction if they were taking more than one drug. Side effects were reported to be experienced by just over 40% of the participants.

It is assumed that these adverse effects were not very severe, as only five participants stopped taking their medicine as a result. Assuming that the original diagnosis of hypertension was correct, the study found that blood pressure was adequately controlled in nearly 50% of all the study participants.

Antihypertensive drug treatment in the Mamre community was mostly appropriately used and controlled 60% of those participants whose blood pressure readings were available from their doctors records, without intolerable side effects. Their treatment did not appear to impact to any great extent on their quality of life, but did appear to be a significant financial burden for those participants who had to pay for their treatment.

A method was therefore developed whereby a sample of patients with a specific disease state from a specific community was identified. Data on drug utilisation were obtained through review of the patient records and structured interviews and the medical, social and economic outcomes of the drugs' use were obtained.

This method and its shortcomings were critically examined. In the process useful data on the utilisation of antihypertensive in the "real life" primary health care setting were obtained.

INTRODUCTION

In order to form the best possible sociomedical and health economic basis from which regulatory and other decisions can be made, audit systems need to be established. In principle such audit systems involve a number of sequential steps. The first is the collection and compilation of the relevant facts; the second involves organisation and analysis of the data; the next step centers around what decision are to be made and subsequently their implementation. The final step is one of re-evaluation, with appropriate adjustments if required (Knoben, 1981).

These types of audits have been termed Drug Utilisation Review studies and serve as a quality assurance process, which in turn promotes rational drug use. Appropriate Drug Utilisation studies are invaluable tools for all involved in drug and health policies and related decision making. They also represent a mechanism for improved communication between health authorities, health personnel and scientists. However, functional systems for conducting such reviews are still lacking in most countries, a situation which could lead to the danger that many important decisions are made arbitrarily and that their consequences are rarely known (Baksaas, 1986). South Africa is no exception to this finding. A recent survey of South African hospitals revealed that only 12% had quality review committees (Summers, 1991) and no such community-based studies could be found in the recent literature.

The expansion of the Pharmaceutical industry since the late 1950's and the resultant plethora of new drug products on the market has created concern for iatrogenic disease associated with drug use (Hutchinson *et al*, 1990), as well as inappropriate drug use. As a result, the need for rationalising drug therapy became an emerging issue. More recently, the cost associated with drug therapy and in particular irrational drug use has added an important new dimension to the clinical decision-making process.

One area in which there has been a surge of new drugs is that of hypertension. These newer agents, such as the ACE-inhibitors and calcium channel blockers, are considerably more expensive than the older agents (thiazide diuretics, reserpine and beta-blockers). These agents have been widely promoted as having comparatively less adverse effects and thereby giving a potentially higher quality of life (Croog *et al*, 1986). There is, however, still some controversy as to the cost-benefit ratio of these agents, especially when used to treat mild hypertension (Johannesson *et al*, 1992; Kawachi, 1992). On the other hand, what are the costs of the side effects and the reportedly poor metabolic profiles of the older agents? Optimal management of hypertension therefore involves finding a balance among its benefits, risks and costs, while ensuring that the adverse effects of the drugs do not compromise patient compliance.

In South Africa, very little is known about the patients' perception of their antihypertensive drug treatment and of the socioeconomic consequences of such treatment. These factors, together with the medical outcomes, form the complete picture of the consequences of treatment for the patient. Before any definitive guidelines can be developed for the management of hypertension in

South Africa, it is imperative that such information is available. It is with this objective in mind that this study was undertaken. Furthermore, it is anticipated that the methodological issues clarified by doing this study will be valuable for designing similar studies involving other chronic diseases.

CHAPTER 1. DRUG UTILISATION REVIEW

1. Definition
2. Differences in prescribing habits
3. The economic consequences of drug use
4. The objective of a drug audit

1. DEFINITION

The World Health Organisation (WHO) defines Drug Utilisation as the marketing, distribution, prescription and use of drugs in society with special emphasis on the resulting medical, social and economic consequences (Grimsson, 1980). This definition does not limit drug utilisation to merely detecting adverse reactions, but extends it to drug efficacy and gives the social and economic consequences equal importance to the medical consequences (Grimmson, 1980). The definition also recognizes that several steps and factors are involved in the drug use process, and that in each of these steps problems in drug use can arise. Factors that may contribute to these problems can have historical, social, organisational, political, economic, technologic, psychologic or pharmacologic origins (Serradell *et al*, 1987). At the moment drug utilisation studies do not cover the broad definition. As early as 1982 Friebel reported that, a decade after this shortcoming was described, drug utilisation studies still deal mainly with the prescription patterns and touch only briefly on the other questions (Friebel, 1982).

2. DIFFERENCES IN PRESCRIBING PATTERNS

There is an increasing awareness of the fact that available drugs are not always used in the best possible way and that there are large differences in the prescribing patterns in the different regions of the same country (Gross, 1975). These differences generally lack rational explanations. Because of large differences in the prescribing and small explanations, it appears important to study these differences and their possible outcomes (Hjort *et al*, 1984). The large differences in the drug utilisation patterns between doctors, hospitals, regions and countries can be, in a small part, accounted for by the differences between individual doctors, hospitals and medical schools. What is observed, however, are large differences and small explanations, (Hjort *et al*, 1984) especially in the view of the fact that doctors have the opportunity to contact one another and exchange opinions through journals, congresses and symposia (Gatti, 1975).

3. THE ECONOMIC CONSEQUENCES OF DRUG USE

The medical consequences of prescribing differences are probably small but they have important economic implications (Hjort *et al*, 1984) especially in todays health services where money matters. The cost impact of drugs must not be defined too narrowly, so as to only include the acquisition cost of the drug. Also to be considered are the costs associated with physician visits, laboratory tests and treatment of drug

induced side effects (Anderson *et al*, 1990). There is increasing pressure on doctors to use the cheapest drug available, unless it can be proven that the more expensive one gives better results. While this may take away the room for both doctor and patient individualisation, it will leave less room for irrational prescribing (Hjort *et al*, 1984). However, policies that encourage the use of drugs carrying the lowest price tag may not always result in the lowest overall health care cost (Anderson *et al*, 1990).

Compounding the problem of the spiralling cost of medicines , is the ever increasing speed and number of new drugs which are appearing on the market (Hitchinson *et al*, 1990) and the societies' belief that there is now "a pill for every ill." In this drug-minded world over-prescribing of drugs is unavoidable, the consequences of which may not be harmful in relation to more or less inactive drugs, but becomes more serious when trivial symptoms or diseases are treated with highly active remedies, the use of which should be limited to the established indication (Gross, 1975). A large number of prescriptions are useless, they do not help the patient, but fortunately they do not harm him either, because the human organism tolerates a lot (Gross, 1975). Nevertheless senseless prescribing is not what medicine is aiming at and should be reduced as much as possible (Gross, 1975). Studies have shown that not all prescribing is based on the patients needs and not all patients needs are met by drug therapy (Serradell *et al*, 1987).

The high cost of medicines and the potential for unwanted reactions require health care professionals to be extremely proficient in their ability to use drug therapy rationally (Hutchinson *et al*, 1990). If the over-riding goal of health care is to improve the health status, then it follows that every health care policy and program must be evaluated in terms of the patients' health status (their quantity and quality of life, their ability to perform personal, occupational and social roles and the burden of physical and psychological symptoms). Drugs through their direct pharmacologic effects can influence health status (Anderson *et al*, 1990). Drug therapy should therefore be monitored for effectiveness and adverse effects. Inappropriate medication may lead to prolonged illness and increased costs (Natiello, 1988). Cost reductions should be accomplished without an unacceptable decline in health status of the population affected (Anderson *et al*, 1990).

4. THE OBJECTIVE OF A DRUG AUDIT

The objectives of a drug audit is to identify problems associated with prescribing and to provide recommendations that lead to solutions for the identified problems (Serradell *et al*, 1987). The theoretical purpose of implementing a program of drug use review, as stated by the U.S. Task Force on prescription drugs, is to establish a dynamic review process aimed firstly at rational prescribing, (the right drug, for the right patient, in the right amounts, at the right time) with the consequent improvement in the quality of care, and secondly at minimizing needless expenditure (Knoben, 1981).

CHAPTER 2. BLOOD PRESSURE CONTROL AND THE PATHOPHYSIOLOGY OF HYPERTENSION

1. The normal physiology of the blood pressure regulating systems in the body

1.1 Short term blood pressure control

1.2. Long term blood pressure control

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(i) Sustained hypertension

(ii) Malignant hypertension

(iii) Rebound hypertension

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1. THE NORMAL PHYSIOLOGY OF THE BLOOD PRESSURE REGULATING SYSTEMS IN THE BODY

Blood pressure is the pressure of the column of circulating blood within the vascular system (Macdonald Critchely, 1980). The term "blood pressure" implies the systemic arterial pressure. Many organs and factors are responsible for normal regulation of blood pressure. The organs involved include amongst others the sympathetic nervous system, kidneys and adrenals (Kochar *et al*, 1979), while the major factors involved are the pumping action of the heart, the viscosity of the blood, the total length of the resistance vessels, the amount of blood in the system and the elasticity of the arterial walls (Kelly *et al*, 1989). These factors are summarised by the hydraulic equation; arterial blood pressure is directly proportionate to the product of the blood flow (cardiac output, CO) and the resistance to passage of blood through precapillary arterioles (peripheral vascular resistance, PVR) (Katzung, 1989).

$$BP = CO \times PVR$$

The pressure in the aorta and in the brachial and other large arteries in a young adult rises to a peak value (systolic pressure) of about 120 mmHg during each heart cycle and falls to a minimum value (diastolic pressure) of about 70 mmHg (Ganong, 1991). Increases in cardiac output, which are determined by the heart rate and stroke volume (amount of blood ejected from the heart per beat) generally result in a raised systolic blood pressure. Diastolic blood pressure, on the otherhand, is influenced by the resistance in the arterioles. The arterioles have a rich supply of sympathetic nerves containing

norepinephrine, which when released act on the smooth muscle cells causing vasoconstriction. Renin, secreted from the kidneys, results in the production of angiotensin II which is a potent vasoconstrictor (Fox *et al*, 1986; Kochar *et al*, 1979).

Physiologically, in both normal and hypertensive individuals, blood pressure is maintained by moment-to-moment regulation of cardiac output and peripheral vascular resistance. The renal and adrenal cortical mechanisms help in the long-range maintenance of normal blood pressure (Katzung, 1989). Baroreflexes act in combination with humoral mechanisms and the renin-angiotensin-aldosterone system, as well as other mechanisms, to coordinate function at these control sites and to maintain normal blood pressure. Regulation of blood pressure in hypertensives differs from normotensives in that the baroreceptors and the renal blood volume pressure control systems appear to be "set" at a higher level of blood pressure.

1.1. SHORT TERM BLOOD PRESSURE CONTROL

Baroreflexes are responsible for the rapid, moment-to-moment, short term adjustments of blood pressure (Katzung, 1989). With increasing age and with increasing levels of resting, mean arterial blood pressure, however, there is a marked decrease in baroreflex sensitivity (Sleight, 1986). The internal pressure of the blood against the vessel wall stretches the vessel wall, which in turn stimulates the carotid baroreflexes. Activation of baroreceptors inhibits central sympathetic discharge, whereas reduction in stretch results in a decrease in baroreceptor firing. When sympathetic discharge is disinhibited the reflex acts through sympathetic nerve endings to constrict the arterioles, therefore peripheral vascular resistance and cardiac output are increased and blood pressure is restored to normal or increases (Katzung, 1989).

The autonomic nervous system (ANS), comprising the sympathetic and parasympathetic systems, plays a dominant role in blood pressure regulation. Increased sympathetic stimulation leads to an increased release of catecholamines (adrenaline and nor-adrenaline) which in turn increases the heart rate and force of contraction of the heart (beta-adrenergic receptors) and also causes constriction of the peripheral arterioles (alpha-adrenergic receptors), while parasympathetic stimulation decreases the heart rate (Paton, 1984; Kochar, 1978). Alpha-1 receptors are located on blood vessels and cause vasoconstriction, while beta-1 receptors are located on the heart and cause an increase in the heart rate as well as an increase in the force of myocardial contraction. The release of noradrenaline therefore results in a rise in blood pressure. Most catecholamines released from the nerve terminals are reabsorbed

and less than 5% are absorbed into the blood and finally excreted in the urine (Sleight, 1986). Despite the large reuptake of noradrenaline, studies have shown that under the same conditions at rest there is a direct correlation between plasma noradrenaline concentrations and the level of diastolic blood pressure (Kiowski *et al*, 1981; Engelman *et al*, 1970; Buhler *et al*, 1980).

1.2. LONG TERM BLOOD PRESSURE CONTROL

The kidney is primarily responsible for long term blood pressure maintenance by regulating the fluid and electolyte balance of the body, thereby homeostatically regulating the extracellular fluid volume (Katzung, 1989). If the arterial blood pressure rises, the kidney excretes more salt and water until it reaches equilibrium at the original blood pressure. Moreover they produce vasoactive substances, kinins and prostaglandins, which are thought to have a local vasodilator action (Buhler *et al*, 1983). Sodium depletion, hypovolaemia, sympathetic neural activity (via beta-adenoreceptors) and the secretion of catecholamines stimulates the kidney to secrete renin. Alteration in tubular fluid composition and vascular stretch also stimulates the production of renin (Katzung, 1989; Kochar, 1978). Renin is responsible for the formation of angiotensin I which is converted to angiotensin II. Angiotensin II is a potent arteriolar vasoconstrictor. In addition, angiotensin II stimulates the sympathetic nervous system and promotes the synthesis of aldosterone in the adrenal cortex. Aldosterone acts primarily at the distal tubule and collecting ducts of the nephron where it enhances sodium absorption and potassium excretion. Sodium retention leads to the expansion of extracelluler volume and elevation in blood pressure. The resultant increase in blood pressure and therefore pressure natruresis has a twofold effect reducing renin release again

and restoring sodium/volume homeostasis (Buhler *et al*, 1983). In the hypertensive patient, pressure naturesis is impaired and blood pressure seems to rise to a point where the sodium balance is restored. There does, however, appear to be a sub-group of patients with essential hypertension who have an inherited or acquired inability of the kidney to handle sodium loads (Stokes GS, 1988).

1.2.1. Renin status of patients with essential hypertension

Radioimmunoassays of the various intermediates of the renin system allow for patients to be classified into high, normal and low renin groups (Brunner *et al*, 1972). Analysis of the renin status of patients with essential hypertension classifies 15% as high renin, 55 - 65% as normal renin, and 20 - 30% as low renin. (Williams, 1991; Laragh, 1980). With increasing age, plasma angiotensin II levels fall and the percentage of patients with high renin levels decline, and the percentage of patients with low renin levels increase (Tuck *et al*, 1973).

Low-renin essential hypertension occurs more frequently in black patients and in older patients (Williams, 1991; Birkenhager *et al*, 1976). These patients are shown to have an expanded extracellular fluid volume, but are not neccessarily hypokalaemic. Involvement of the adrenal cortex in low-renin hypertension, is suggested by the observation that large doses of mineralocorticoid antagonists (eg. spironalactone) and inhibition of steroidgenesis by aminoglutethimide can result in sodium loss and the lowering of blood pressure in these patients. It has also been postulated that these patients have an increased sensitivity of

their adrenal cortex to angiotensin II (Williams, 1991). The fact that low-renin hypertensive patients are significantly older (aproximately 9 years) than patients in the other two sub-groups, even though they often have higher blood pressures, suggests that they enjoy some measure of protection from cardiovascular damage, namely atherosclerotic diseases eg. ischaemic heart disease, peripheral vascular disease and cerebrovascular disease (Laragh, 1980).

In high-renin essential hypertension it is suggested that the elevated renin levels and blood pressure, may both be secondary to an increased activity of the adrenergic system (Willliams, 1991). High renin essential hypertension is often termed angiotensin dependant hypertension. These patients are often younger with greater variability of blood pressure, heart rate and cardiac output (Burkart *et al*, 1976).

1.3. CARDIAC OUTPUT AND ARTERIOLAR RESISTANCE

Reactive hypertrophy of the myocardium and of the vascular smooth muscle occurs as a function of blood pressure elevation and time. This becomes an important homeostatic mechanism for helping to maintain the blood pressure in all forms of hypertension (Stokes GS, 1988). Vascular smooth muscle hypertrophy may occur in part because of a disturbance of cell growth, contingent upon primary changes in cell membrane function (sodium-hydrogen countertransport) in essential hypertension (Lever AF, 1986). Changes in cell membrane cation transport in essential hypertension have also been postulated to lead to increased vascular smooth muscle contractility by increasing intracellular calcium concentration (Stokes GS, 1988).

2. THE PATHOPHYSIOLOGY OF HYPERTENSION

2.1. CLASSIFICATION OF HYPERTENSION

High blood pressure is not clearly defined. Arbitrary levels have been established to define those who have an increased risk of developing a morbid cardiovascular event and/or will clearly benefit from medical therapy (Willliams, 1991). The Heart Foundation of South Africa suggested that hypertension in adults of any age is defined as a persistently elevated systolic blood pressure of more than 160 mmHg and / or a diastolic pressure of more than 95 mmHg (Heart Foundation, 1992).

2.1.1. Essential Hypertension

"Essential hypertension" is defined as blood pressure elevation stemming from a progressive rise in pressure with age for which there is no obvious cause (Beilin L, 1989). This definition is correct for 95% of cases of so-called hypertension.

(i) Malignant Hypertension:-
refers to a patient in which the blood pressure suddenly rises, and the disease accelerates from its slowly progressive form (Sleight P, 1986). This increase is accompanied by papilloedema, usually retinal haemorrhages and exudates, proteinuria, haematuria and progressively impaired renal function (Mitchell J.R.A., 1989). The small arteries are

destroyed by fibrinoid necrosis, and such patients usually have diastolic pressures of 120 mmHg or above.

(ii) Accelerated Hypertension:-
signifies a significant recent increase over previous hypertensive levels associated with evidence of vascular damage on funduscopic examination but without papilloedema.

(iii) Sustained Hypertension:-
is thought to result from the "resetting" of the carotid sinus baroreceptors so that the homeostatic mechanism tends to maintain rather than combat increased arterial pressure.

(iv) Rebound Hypertension:-
is a syndrome which follows the abrupt withdrawal of certain types of antihypertensive treatment such as clonidine and the beta-adrenergic antagonists (Robertson *et al*, 1986).

2.1.2. Secondary Hypertension

Patients with a specific organ defect responsible for hypertension are said to have secondary hypertension (Williams, 1991). Nearly all the secondary forms are related to primary aldosteronism, Cushing's syndrome, pheochromocytoma, exogenous hormones eg. oral contraceptive pills and/or renal function. These cases comprise no more than 10% of the hypertension present in the Westernised communities (Stokes,G.S. 1988).

CHAPTER 3. EPIDEMIOLOGICAL CLUES TO THE AETIOLOGY OF HYPERTENSION

1. Introduction
2. Heredity
3. Stress
4. Salt
5. Obesity
6. Age and sex
7. Race
8. Exercise
9. Smoking
10 Alcohol
11. Blood lipids
12. Impaired glucose tolerance
13. Insulin resistance

Chapter 3. Epidemiological clues to the aetiology of hypertension

1. INTRODUCTION

The cause of essential hypertension is multifactorial (Beilin,L. 1989). Factors such as obesity, alcohol consumption, diet and physical inactivity play a major part in the elevation of blood pressure, each operating against a background of varying genetic susceptibility. These variables in addition to the level of arterial pressure per se modify the course (Wilson JD *et al*, 1991). Thus, the risk of developing a morbid cardiovascular event with a given arterial pressure may vary by as much as twentyfold depending on whether associated risk factors are present (Wilson JD *et al*, 1991).

Hypertension is one of several risk factors for cardiovascular disease and should always be assessed and treated in the context of the other existing risk factors.

2. HEREDITY

Genetic factors have long been assumed to be important in the genesis of hypertension (Wilson JD *et al*, 1991). Data supporting this view can be found in both animal as well as population studies in humans. Hypertension tends to run in families (Pickering, 1968) and studies of identical twins in different environments support this fact (Miall, 1963).

3. STRESS

Despite the extensive literature on psychological factors, it is still not clear whether they play a significant part in the long-term blood pressure regulation, though there is no doubt that the emotional factors can induce pronounced but transient variations in blood pressure (Beilin L. 1989).

The influence of stress due to urbanisation is difficult to separate from the influence of increased dietary salt intake and the adoption of a western diet.

4. SALT

Dietary sodium intake of most developed countries varies from 100 -300 mmol/person/day, which is in excess of normal physiological requirements (Beilin L, 1989). Randomised controlled trials of the effects of sodium restriction to 70 -90 mmol/day suggest significant blood pressure reductions of the order of 3 -5 mmHg systolic pressure in hypertensives. The blood pressure reduction is most clear cut in older subjects, in patients with moderate or severe hypertension and salt reduction increases the effectiveness of most other antihypertensive drugs, for example, diuretics and angiotensin converting enzyme inhibitors (Swales JD, 1989; Beilin L, 1989). Levels of dietary sodium and potassium are generally inversely related, as populations with high salt intake tend to eat little in the way of fruit and vegetables (Beilin L, 1989). Cross-sectional population studies suggest that dietary potassium has a blood pressure lowering effect, and that estimates of dietary

sodium:potassium ratios are more strongly associated with blood pressure levels than their cations independently.

5. OBESITY

There is a continuous linear relationship between excess body fat, blood pressure levels and the prevalence of hypertension (Messerli F.H., 1986). An increase in body mass requires an increase in cardiac output and intravascular volume to fulfil metabolic requirements. This increase, however, exceeds by far the amount needed to perfuse excessive adipose and supportive tissue. The effect of obesity on blood pressure appears to be additive to that of alcohol consumption, and may be compounded by physical inactivity and specific dietary components, such as high salt intake (Beilin L, 1989). As obesity also contributes to blood lipids abnormalities and impaired glucose tolerance, it has particular significance as a factor underlying the increased prevalence of coronary artery disease in hypertensive patients. A weight loss of 3 kg reduces blood pressure by approximately 7 mmHg systolic/4mmHg diastolic and a weight loss of 12 kg gives a fall of 21/13 mmHg (Swales J.D. 1989).

6. AGE AND SEX

Elderly hypertensive patients are usually characterised by a low cardiac output and, as a consequence, by a very high total peripheral resistance (Messerli F.H., 1986). In the elderly, the left ventricle is burdened with a high afterload which accelerates the age-induced decline of left ventricular performance. The more severe the arterial hypertension, the faster left

ventricular function declines and the earlier the stage of congestive heart failure will be reached. At the same time, renal blood flow often falls even faster than systemic blood flow because of progressive nephrosclerosis. In parallel with the increase in total peripheral resistance, intravascular volume becomes more and more contracted. This volume contraction makes elderly hypertensive patients particularly susceptible to volume depletion. Circulating noradrenaline levels are usually elevated, whereas plasma renin activity has been shown to be low and less responsive in elderly hypertensive patients, unless congestive heart failure is present. Except for some primitive societies, hypertension is extremely common in the elderly and a disproportionate rise in systolic pressure with age is usual so that isolated hypertension is quite common (Kannel WB. 1986). Whatever the variety of hypertension in the elderly, it is clearly dangerous from the standpoint of absolute risk, risk gradients and attributable risks. Cardiovascular mortality is tripled in the hypertensive elderly compared to normotensives of the same age (Kannel WB, 1986).

Blood pressure in women rises with age but at a lower level than men until the menopause, when it reaches the male level (Stokes, 1988). Despite this factor there is no evidence that women tolerate hypertension well at any age (Kannel, 1986).

7. RACE

Hypertension is more prevalent in blacks than whites, and systemic vascular and target organ disease such as hypertensive heart disease, stroke and nephrosclerosis is also more rapid and severe (Messerli F.H., 1986). However there is not a significant difference in cardiac output, total peripheral resistance or intravascular volume between blacks and whites with essential hypertension. On studying renal and hepatic blood flow, it was found that hepatic blood flow was similar in blacks and whites, but renal blood flow was lower and renal vascular resistance was higher at any level of renal arterial pressure in blacks. Black patients also had increased left ventricular mass when compared with white patients that were matched with regard to mean arterial pressure (Masserli FH, 1986).

8. EXERCISE

There is good evidence that regular physical exercise may reduce blood pressure substantially (Swales JD, 1989). Individuals who undertake regular physical exercise have lower blood pressures than sedentary people (Beilin L, 1989).

9. SMOKING

Smoking does not itself lead to hypertension but it greatly increases the vascular complication rate in people with hypertension (Simpson FO, 1988). The MRC Working Party (UK, 1985) and the Australian National blood Pressure Study

(1980) showed very clearly that in very mild hypertension the benefits of not smoking are greater than those of antihypertensive drug treatment. The risks carried by a hypertensive patient who smokes are additive to the risk of hypertension (Swales J.D. 1989). Smoking leads to an acute elevation of blood pressure, though the effect usually subsides within 15 minutes of finishing a cigarette unless combined with strong coffee, when it may persist for up to 2 hours (Beilin L, 1989). Regular smokers tend to have a slightly lower blood pressure than non smokers, largely because they tend to be slimmer. Unfortunately, the small potential benefit of this effect is greatly outweighed by the adverse effects of smoking on coronary heart disease and other pathologies (Beilin L, 1989).

10. ALCOHOL

Alcohol has recently emerged as another major contributor to blood pressure elevation (Beilin L, 1989). The relationship appears to be linear above 10 - 20g ethanol equivalent per day. (i.e. 1-3 standard drinks per day) (Editorial; Annals of Int. Med., 1986). People who have three or more standard drinks per day have a threefold increased prevalence of mild hypertension compared with non-drinkers. Reducing alcohol intake by 80% can result in a significant and reversible fall in blood pressure within 1-2 weeks. There is no justification for advising moderate drinkers to abstain totally (Swales JD, 1989).

11. BLOOD LIPIDS

The lipoproteins play a central role in the atherosclerotic process accelerated by hypertension (Kannel WB, 1986). The well established positive relation of the serum total cholesterol to coronary heart disease incidence is now recognised as a direct consequence of the low density lipoprotein (LDL) cholesterol component. The high density lipoprotein (HDL) cholesterol fraction involved in removal of cholesterol from the tissues has been shown to be inversely related to the occurrence of coronary heart disease. It was originally thought that the VLDL (very low density lipoprotein) cholesterol did not contribute to artherogenesis (Kannel, 1986), but patients with high VLDL may infact have increased risk for premature atherosclerosis when associated with other risk factors for coronary artery disease, such as diabetes, smoking and hypertension (Wilson, 1991).

12. IMPAIRED GLUCOSE TOLERANCE

Diabetes is often associated with a poor cardiovascular risk profile including blood pressure, reduced HDL cholesterol and obesity (Kannel WB, 1986). The risk of coronary heart disease in hypertensives is enhanced by diabetes, and the risk of every clinical manifestation of the disease is greater in the diabetic hypertensive than in the non-diabetic. The relative impact is greater in women than men. Diabetes also directly damages the myocardium so that hypertensive cardiac failure is more likely to occur than in the non-diabetic with hypertension (Kannel WB, 1986).

13. INSULIN RESISTANCE

Insulin resistance is generally interpreted as the physiological state under which insulin causes a reduced glucose lowering effect, while hyperinsulinaemia is considered to be a result of insulin resistance (Baba T & Neugebauer, 1994). The aetiology of resistance to insulin-stimulated glucose uptake is unknown, although it is probably under genetic control (Ferrannini & Defronzo, 1989). Insulin is thought to raise the blood pressure by a few possible mechanisms (eg. stimulating sympathetic nervous system activity and enhancing renal tubular sodium reabsorption)(Young JB, 1988; Treisan M *et al*, 1988). On the other hand insulin has been reported to possess a vasodilatory property (Hall JE *et al*, 1990). Neither an insulin infusion within a physiological range nor continuously sustained hyperinsulinaemia in patients with insulinaemia are associated with elevated blood pressure. The relationship between insulin and blood pressure is therefore still under discussion, and there seems to be insufficient evidence to prove that insulin *per se* can raise blood pressure in humans (Baba T & Neugebauer S, 1994). However, epidemiological evidence suggests a link between hypertension, diabetes, adiposity and an abnormal lipid profile and that the prevalence of each disease increases with age (Ferrannini *et al*, 1990; Reaven GM & Hoffman BB, 1987), referred to as syndrome X. Age has been suggested to parallel a decrease in the whole body insulin-stimulated uptake of glucose (De Fronzo RA, 1981). Obesity studies have suggested that the peripheral insulin sensitivity is decreased by up to 30 - 40% in individuals with more than 130 -140% of ideal body weight and in nondiabetic individuals who gained their weight by an excessive caloric intake (Ferrannini E & De Fronzo RA, 1989).

CHAPTER 4. THE PROBLEMS OF HYPERTENSION AND THE TREATMENT OF HYPERTENSION

1 Prevalence of hypertension in South Africa

2. The aim of hypertension treatment

3. Management of hypertension

4. When to start drug treatment

5. Compliance problems

6. Reduction in morbidity and mortality due to treatment

7. Antihypertensives suitable for initial therapy

1. PREVALENCE RATES IN SOUTH AFRICA.

Hypertension remains a major health concern in the industrialised world and much of the third world. Persons with hypertension are at excessive risk for cardiovascular disease, coronary heart disease, congestive heart failure and renal failure. The prevalence of hypertension varies widely around the world and these differences can be attributed in part to environmental differences including life style (Grimm, 1991).

Epidemiological studies in South Africa suggest that hypertension, where blood pressure is greater than or equal to 160/95mmHg, is common among urbanised South Africans or those who follow a typical westernised lifestyle (Steyn, 1991). On the basis of the 1991 Census it was estimated that approximately 6,5 million South Africans have a blood pressure above 140/95mmHg and approximately 3,2 million have a blood pressure above 160/95mmHg (Heart Foundation, 1992). The prevalence of hypertension differs in the various population groups of Southern Africa. In the urban zulu it has been quoted as high as 25% compared with 10% in the rural zulu. In urban Indians it is 19%, in the urban whites 23% and in the rural whites 26%. The presence in the urban coloured population is 28% (Steyn *et al*, 1990). Various epidemiological studies in South Africa have confirmed that hypertension is inadequately diagnosed and treated, suggesting the need for improved population based management in South Africa (Steyn, 1991).

2. THE AIM OF HYPERTENSION TREATMENT

In the vast majority of cases the cause of hypertension is still not known, but in about 5-10% of cases hypertension is secondary to some known pathological condition or drug induced (Seedat,1991). All other patients have essential or primary hypertension - a persistently raised blood pressure with no underlying cause (Kendle, 1989; Seedat, 1991). A persistent elevation of blood pressure above 90-95mmHg for diastolic pressure, is found to be associated with an increase in cardiovascular morbidity and mortality (Venter, 1990), therefore the basic principle of drug treatment is to lower the patient's blood pressure to an acceptable level with the minimum interference to his or her well being. However, there are no studies that show a beneficial effect of drug treatment if the initial DBPwas less than 105 mmHg. The aim of antihypertensive treatment is to obtain normotension and to reduce cardiovascular risk, thereby preventing coronary heart disease, stroke and death. The clinical end point is the regression of the left ventricular mass, the prevention of renal damage and of retinal haemorrhages (Nieminen, 1991).

3. MANAGEMENT OF HYPERTENSION

There are two modes of treatment which must be combined; non drug treatment and drug treatment. Non-pharmacological methods may be used as sole treatment for borderline or mild elevation of blood pressure or as an adjunct to pharmacological therapy. These measures involve weight reduction, alcohol and smoking cessation, reduction of salt intake and the promotion of exercise

(Hansson et al, 1990). Drug treatment of patients whose diastolic blood pressure dose not exceed 100mmHg is likely to cause more problems than benefits, unless there are secondary factors to consider such as diabetes or hyperlipidaemia (Hepburn et al, 1990).

4. WHEN TO START DRUG TREATMENT

It is advocated that hypertension should ideally be detected as early as possible and treated aggressively to avoid target organ damage and all its consequences (Venter, 1990). Non drug treatment is indicated for the total population whatever the blood pressure (except the rare person with pathological hypotension). It is more difficult, however, to decide when to start drug treatment. It will probably vary according to factors such as age, sex, population group and other cardiovascular risk factors. South African Hypertension Society suggest that in South Africa it would be appropriate to start non drug treatment if the diastolic blood pressure was 95mmHg or greater and only to initiate drug treatment if there were co-existing risk factors for cardiac disease or if no response is obtained from non drug treatment after 3-6 months. Non pharmacological measures should be maintained, in addition to drug treatment (Heart Foundation Concensus, 1992). The British Hypertension Society's recommendations are not to initiate drug therapy unless the diastolic blood pressure is greater than or equal to 100mmHg and the patient has other risk factors for vascular disease (British Hypertension Society Working Party, 1989). The American Joint National Committee on hypertension recommend an intermediate position of 95mmHg for diastolic blood pressure

(Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure, 1988). There is reasonable consensus that antihypertensive drugs should be given to patients up to the age of about 75-89 years if their diastolic pressure is consistently over 95-100mmHg for a period of four months (Hansson et al, 1990). The South African Hypertension Concensus Document recommends non-pharmacological management for all patients with a blood pressure above 140/95 and drug plus non-drug treatment for those with a blood pressure above 160/95 and evidence of end-organ damage or coexisting risk factors. The goal blood pressure should be the same as that for initiation of treatment, however, if there is evidence of end-organ damage or other coexisting risk factors for cardiovascular disease then the goal blood pressure should be <140/90mmHg, irrespective of the baseline blood pressure level (Heart Foundation, 1992). It has been suggested that the lowering of diastolic blood pressure below 85mmHg predisposes patients with ischaemic heart disease to myocardial infarction, though the evidence for this is still controversial (Swales, 1989; Fletcher *et al*, 1991). Isolated systolic hypertension is initially treated non-pharmacologically, however, when the systolic blood pressure is consistently 160mmHg or greater and the diastolic pressure is less than 90mmHg, despite non-drug measures, then antihypertensive drug treatment should be considered (Seedat, 1991).

5. COMPLIANCE PROBLEMS

Lowering of the blood pressure by using pharmacological agents is not an innocuous procedure and may even have serious consequences on the mortality and morbidity, if not done discreetly and carefully (Venter, 1990). Probably the most difficult aspect of long term antihypertensive therapy is that while the disease is relatively asymptomatic, the adverse effects of therapeutic lowering of blood pressure with drugs are numerous, often requiring an alteration of the patients life style (Morse et al, 1986). The adverse effects may influence the quality of life to such an extent that the treatment of hypertension may be worse than the disease and its consequences and it may thus have negative effects on compliance (Venter, 1990).

6. REDUCTION OF MORBIDITY AND MORTALITY DUE TO TREATMENT

Seftel asks the question of why we consider treating mild hypertension and in doing so transform a mass of people into patients with all its physical, psychological, social and economic implications (Seftel, 1991)? The answer lies in the fact that most trials have clearly been shown to reduce cardiovascular morbidity and mortality. A 40-50% reduction in stroke has been demonstrated, but unfortunately very little effect on coronary heart disease was noted (Hansson et al, 1990). A recent meta-analysis of the drug trials in hypertension indicated that 5-6mmHg reduction in diastolic blood pressure, maintained for a few years, produced a 14% reduction in coronary events (expected 20-25%). Mac Mohan et al calculated that a 10mmHg lowering of

diastolic blood pressure was associated with at least 56% less stroke and 37% less coronary heart disease (Mac Mohan et al, 1990). On the other hand the British Medical Research Council (MRC) trial suggested that 850 low risk patients would have to be treated for one year to prevent one stroke (MRC Working Party, 1985) and the Australian National Blood Pressure Survey showed a saving of two lives per 1 000 patient years of treatment (Louis, 1991).

7. ANTIHYPERTENSIVE COMPOUNDS SUITABLE FOR INITIAL THERAPY

The fact that not all patients respond equally well to all antihypertensive drugs and the introduction of the calcium channel antagonists and the angiotensin converting enzyme (ACE) inhibitors have challenged the rigid "stepped-care" approach for drug treatment of hypertension. Four groups of antihypertensive drugs are regarded as equally suitable for the first step of antihypertensive therapy: angiotensin converting enzyme inhibitors, beta-blockers, calcium antagonists and diuretics. This view is supported by recommendations from the Joint National Committee (JNC) in the USA, the World Health Organisation and the International Society of hypertension (Hansson et al, 1990). The South African Hypertension Society finds the recommendations of the JNC generally applicable to the local situation, but stresses that the cost of treatment should also be considered together with the patient as a whole in their social setting (Heart Foundation, 1992). Patients should ideally start with a single drug in the smallest effective dosage. Combination therapy is indicated if monotherapy fails, as most antihypertensive drugs act synergistically and frequently counter each others unwanted effects (Venter,

1990). All classes contain extremely useful drugs which benefit individual groups of patients and have all been shown to be efficacious. Once the blood pressure has been normal for a year or more, a cautious decrease in antihypertensive drug dosage and renewed attention to non-pharmacologic treatment may be worth trying (Abramowicz, 1989).

There remain however many areas of controversy in the treatment of uncomplicated essential hypertension. Some trials have suggested that diuretics may actually increase the infarction and sudden death rates in hypertensives due to their effect on blood electrolytes and lipids (Raftrey, 1991). Given the large differences in the cost of treatment with different classes of antihypertensives, an assessment of factors such as cost effectiveness and quality of life parameters becomes essential. A question that therefore needs elucidation is if treatment with the more expensive agents (eg. ACE inhibitors) is associated with tangible differences in these factors and more specifically should they replace traditional agents such as the thiazide diuretics as first line therapy in the average case of uncomplicated hypertension (Louis, 1991).

CHAPTER 5. FACTORS WHICH INFLUENCE THE TREATMENT AND CONTROL OF HYPERTENSION

1. Introduction
2. Factors associated with the patient
3. Factors associated with the prescriber

1. INTRODUCTION

There are many practical problems in the treatment of hypertension, namely to get the right patient under treatment and then to treat them properly. Furthermore, little is known about the behavior and ideas of patients and practitioners which can profoundly influence the treatment and therefore the control of hypertension.

2. FACTORS ASSOCIATED WITH THE PATIENT

Patient factors such as age, sex, race, weight, renal function, pregnancy, mental status and attitude towards the disease may all be important variables to consider in selecting drug therapy as this may reveal how a patient will comply with the therapy (Stewart, 1981). Most patients do not have perfect compliance and take about 70-80% of their prescribed treatment, with compliance improving immediately before a clinic visit - the so called "toothbrush effect" (Pullar *et al*, 1990). Non-compliance with prescribed medication regimens is a major problem, especially in the management of chronic disease states such as hypertension, where the disease is manifest by symptoms or is often symptomless (Stewart, 1981). Inadequate compliance may lead to treatment failure, which is obviously of great importance and even potentially fatal for the individual. The reasons for poor compliance could be that patients do not understand the instructions, that they forget to take their treatment or that they have made a decision not to do so. This may be related to factors such as complex drug regimens, (eg. multiple medication use

and frequent dose regimens) poor packaging of the drug or inadequate advice on the importance of compliance with the drugs. The conscious decision not to take the prescribed medicines may be due to fear of possible adverse effects which the patient does not want to discuss with the physician or dissatisfaction with their doctor or medical service (Pullar *et al*, 1990). Lastly the cost of hypertension treatment is not limited to drug costs, but also includes doctors fees, absence from work and transport costs. This cost-benefit ratio is a critical factor in the compliance of many patients (Opie, 1989).

3. FACTORS ASSOCIATED WITH THE PRESCRIBER

Physician prescribing is perceived by many patients to be the major reason for visiting primary care doctors (Anderson *et al*, 1990). Physicians' diagnostic and therapeutic skills will be major determinants as to whether the correct drug is prescribed for the appropriate indication and in the appropriate dose (Stewart, 1981). Various factors such as input from the patient, commercial sources, colleagues, universities, academic literature and government regulators will influence the prescribing patterns (Soumeria *et al*, 1989). Because many of the prescription drugs commonly used today were only approved for use in the last 10-15 years, doctors who graduated from medical school before the release of these drugs may not have been exposed to formal education on the benefit and risks associated with these medicines. The pharmaceutical industry therefore plays an active role in educating the doctors by devoting substantial resources to informing doctors of the benefits

of their products (Anderson *et al*, 1990). A wide variety of factors may contribute to inappropriate prescribing decisions such as failure of doctors to keep abreast of developments in pharmacology, overpromotion of drugs by the pharmaceutical sales representatives and simple errors, oversights or omission. The doctors ignorance of (or apathy) towards cost issues and insulation of the doctor and patient from cost considerations because of third party coverage may further contribute to the problem. Pressure from patients, families or other health workers for a particular drug regardless of indication, overreliance on clinical experience versus scientific data, the doctors need to provide some treatment for problems with no clear medical solution and the tendency to use prescriptions as a "termination strategy" to keep visits short (Soumerai *et al*, 1989) also influence prescribing decisions.

CHAPTER 6. HYPERTENSION IN MAMRE

1. Description of the Mamre community
2. Morbidity and mortality profiles
3. Prevalence rates of hypertension

1. DESCRIPTION OF THE MAMRE COMMUNITY

Mamre was established by the Moravian Church in 1808. It is a small community, of approximately 5 000 inhabitants, situated on the west coast 48km from Cape Town. Mamre is in a state of transition and accelerated urbanisation caused by the encroachment of Cape Town and Atlantis (KLopper *et al*, 1988).

Recently the Department of Community Health at the University of Cape Town and the Centre for Epidemiological Research (CERSA) of the Medical Research Council (MRC) set up a long-term community based study in this urbanising community with the overall aim of improving the health status of the people of Mamre and developing an approach to health promotion which may be applicable to other similar areas (Klopper *et al*, 1989).

2. MORBIDITY AND MORTALITY PROFILES

The need for quantitative information on the health status of the communities, their use of health services and the socioeconomic and environmental factors affecting health, is well recognised. Such information is critical for the appropriate development of health services and the future attainment of optimal levels of health in South Africa (Hoffman *et al*, 1988).

In 1986 Benatar's report on medicine and health care in South Africa described the disease and mortality profile of the coloured population in comparison to the profile of developing countries (Benatar, 1986). Coronary heart disease, common among South African whites, is increasingly manifesting itself in the coloured community (Steyn and Fourie, 1990). Analysis of the mortality statistics for Mamre) from the Regional Services Council records) for 1981-1987 reveals that accidents or violence were the major cause of death. The most common natural cause of death in the community was circulatory disease (Bourne *et al*, 1988). Investigations of several chronic conditions for which people said that they were receiving treatment, yielded rates of 57/1 000 for hypertension, 29/1 000 for "nerves", 13/1 000 for diabetes, and 19/1 000 for tuberculosis. The fact that reported rates of hypertension and diabetes were low is likely to be due to undetected cases in the community (Hoffman *et al*, 1988).

3. PREVALENCE RATES OF HYPERTENSION

The Mamre Community Health Project presents an ideal opportunity to assess disease patterns and health-related issues in a well defined community. In a follow-up study in which women between the ages of 25 and 64 years had their blood pressure measured, an overall prevalence rate of 25.9% was found. Age specific rates were 16.1% for the 24 to 44 year group and 38.4% for the 44 to 64 year group (Marshall *et al*, 1988). The CRISIC study which examined blood pressure among the coloured population of Cape Town reported a prevalence of 18.4% for females between 15 and 64 years. When these rates

were adjusted against international reference populations the prevalence in these coloured women was found to be 26% (Steyn *et al*, 1986). A disturbing finding in the Mamre community was that despite a good overall reported compliance of 72.2%, more than half the subjects on treatment (54.3%) were inadequately controlled. One can either conclude that the medication was not been taken correctly or that the treatment regimens were inappropriate (Marshall *et al*, 1988).

The findings in Mamre are in keeping with other prevalence studies in the coloured population, namely that the prevalence of hypertension is high and up to 50% of patients on treatment are inadequately controlled (Marshall *et al*, 1988). The fact that hypertension is underdiagnosed, undertreated and poorly controlled is characterised by the "rule of halves," which states that:- only approximately half of hypertensives have ever been diagnosed, of which only half receive antihypertensive treatment and about half of those on treatment are adequately controlled (Smith *et al*, 1987).

CHAPTER 7. RESEARCH DEFINITION

1. General aim

1.1. Specific aim

2. Objectives

3. Research methods

3.1. Setting

3.2. Test population

3.3. Sample size

3.4. Sampling

3.4.1. Inclusion criteria

3.4.2. Exclusion criteria

3.5. Data collection

3.5.1. The questionnaire

3.5.2. Patient data

(i) Background data

(ii) Process data

(iii) Outcome data

(a) Medical

(b) Social

(c) Economic

3.5.3. Prescriber data

3.6. Survey procedure

3.6.1. Development phase

3.6.2. Data collection

3.6.3. Evaluation and analysis

3.6.4. Feedback and re-evaluation of criteria

3.6.5. Reassessment

3.7. Choice of interviewers

3.8. Training of interviewers

3.9. Pilot study

3.10. Ethical considerations

1. GENERAL AIM

To develop and evaluate a methodology for a Drug Utilisation Review in Primary Health Care.

1.1. SPECIFIC AIM

In order to achieve this general objective a pilot study was undertaken in the Mamre community with the following aim:
to develop a method to evaluate the use and medical and socioeconomic implications of antihypertensive drug treatment in the Mamre community.

2. OBJECTIVES

2.1. To determine baseline data (see Appendix I) on the use of antihypertensive drugs in the Mamre community.

2.2. To establish background data on both the patients and the prescribers.

2.3. To compare the data on the use of antihypertensive drugs in the study population against the predetermined explicit criteria (Appendix I, 7).

2.4. To assess the medical and socioeconomic consequences of the use of antihypertensive drugs in the community.

2.4.1. To assess the number of hypertensive patients in the sample population whose blood pressures are controlled on their medication.

2.4.2. To identify known side effects of antihypertensive drug treatment that are most troublesome to the study population.

2.4.3. To obtain an approximate estimation of the patients reported compliance on their treatment.

2.4.4. To assess the patients attitude towards their antihypertensive drug treatment.

2.4.5. To obtain a measure of the patients perception of the influence of their antihypertensive medicine on their quality of life.

2.4.6. To assess the cost of treatment for the patient.

2.4.7. To establish the average cost of treatment for hypertension in the Mamre community.

It is intended that the methodology achieved in this instance will be applicable to other similar studies. There may also be the possibility of using the data generated by the study for the formulation of health policy regarding antihypertensive drug use in a specific setting.

3. RESEARCH METHODS

3.1. SETTING

The study was conducted in Mamre, a village of approximately 5 000 inhabitants, which was established as a Moravian Mission Station in 1808. It is situated 48kms up the west coast from Cape Town and 5kms north of Atlantis.

3.2. TEST POPULATION

Mamre is a well established coloured community with strong traditions and it is considered representative of a community undergoing rural-urban transition.

3.3. SAMPLE SIZE

A statistician at the Institute of Biostatistics at the MRC was consulted in order to determine the sample size. A sample size of approximately 200 was deemed appropriate.

3.4. SAMPLING

3.4.1. INCLUSION CRITERIA

The following criteria determined the patient's inclusion in the study:-

(i) the patient must be resident in Mamre

(ii) the patient must have been diagnosed by a doctor as having essential hypertension (i.e. the patient must have consistently exhibited a blood pressure above 160/95 and if possible where other causes have been excluded.)

(iii) the patient must have been on antihypertensive treatment for a minimum of three months and must currently be on that treatment.

(iv) the patient must be 35 years or older.

3.4.2. EXCLUSION CRITERIA

The following criteria determined the patient's exclusion from the study:-

(i) pregnancy

(ii) hypertension resulting from another cause

(iii) treatment for less than three months or a change in treatment in the last three months.

(iv) patients currently not on treatment

A list of patients, over 35 years, believed to be receiving treatment was drawn up from the following sources:

(i) identified hypertensives from the baseline study (1986), the follow-up study of hypertensive women (1987) and the follow-up study of newly diagnosed hypertensives (1991) compiled by the Department of Community Health at the University of Cape Town.

(ii) patients who attend the Mamre blood pressure station

(iii) hypertensive patients who attend the Atlantis Day Hospital satellite clinic in Mamre

(iv) hypertensives on treatment who are identified by the local clinic sisters, doctors and District Surgeons.

A total of 247 hypertensive patients were listed and all were included in the study sample.

3.5. DATA COLLECTION

The required data was collected:-

(i) by means of an interviewer-administered questionnaire.

(ii) from the patient's medical record or folder

(iii) from the Register of Medical Practitioners (1991) compiled by the South African Medical and Dental Council.

3.5.1. THE QUESTIONNAIRE (appendix II)

The questionnaire (appendix II) was drawn up according to the objectives of this study. It was translated into Afrikaans because this is the home language of the majority of Mamre residents.

The questionnaire was divided up into 3 sections:

(i) patient-related demographic data

(ii) process data on drug use

(iii) outcome data, which was further divided into 3 sections:-

questions pertaining to social implications

questions pertaining to economic implications

questions pertaining to medical implications.

Consideration was given to the sequence of the questions. Very personal questions, such as those relating to the participant's sex life, were positioned at the end of the questionnaire. Although the questionnaire was 8 pages long, it took on average 15 to 20 minutes to be filled out by the field worker. Two types of questions were used:-

(i) Closed-ended questions, where the respondent was asked to select an answer from a list provided, were predominantly used. It was felt that this type of question would result in

less variability between the two fieldworkers and could therefore be uniformly interpreted by the researcher.

(ii) Open-ended questions or free response, where the respondents reply in their own words. This question form was used when it was not desirable to prompt or when further comments on a closed-end question were required.

3.5.2. PATIENT DATA

3.5.2.1. BACKGROUND DATA

The data was collected by means of a interviewer-administered questionnaire, in order to record the patient's place of residence, age, sex, highest level of education and any other diseases that he/ she may suffer from. The information on the other diseases was also checked against the doctors' records if these were available or with the records of the Mamre blood pressure clinic when no patient records were available from their regular doctor.

Information on the level of education was recorded as this factor has been shown to influence the degree of compliance. Data on other diseases the patient suffers from is important in view of the fact that diseases such as diabetes and arthritis complicate the management of hypertension and affect patient compliance.

3.5.2.2. PROCESS DATA

The questionnaire recorded where the patient receives treatment and the name of their doctor. These data were needed in order for the researcher to confirm the information supplied by the patient against the doctor's records and to establish the different prescribing patterns amongst the prescribers.

The patient was asked what medicines they were taking, with the assistance of a tablet identification chart and how they were taking these medicines (i.e. dose, route, frequency of administration and duration of treatment). These data were checked, where possible, with the treatment written up by the doctor in the patient's records. The degree of concurrence between the patient-supplied data and the doctor's records was used to estimate the patient's compliance with treatment. One hundred percent concurrence was designated as compliant; poor or no concurrence was designated non-compliant and if the drug could not be indentified but how it was taken described and this found to be compatible with the doctors' notes then the patient was termed probably compliant.

The use of other medicines, either prescribed or over-the-counter, were also recorded in this part of the

questionnaire in order to determine possible drug interactions. Two reputable reference books namely; Hansten's Drug Interactions (5th ed.) and Stockley's Drug Interactions (2nd ed.) were used to establish any predictable interactions.

3.5.2.3. OUTCOME DATA

(i) Social:

The questionnaire was also used to establish the effect of treatment on the patients' daily life style (i.e. their quality of life), their attitudes towards the medical service they use and how they feel on their treatment for high blood pressure.

(ii) Economic:

The questionnaire established the employment status of the sample population and who was responsible for the payment of medicines in this population. The cost of treatment to the patient was documented, if the patient paid for medicines. The cost of medicines paid for by medical aid schemes, was recorded as the retail price and was calculated using the retail pharmacy program *Pharmassist*. Medicines supplied by the District Surgeons or the Government Hospitals were costed from the Cape Provincial Administration's

hospitals tender price list. The data will not be enough to establish cost-benefit ratios, as the study is not a longitudinal one. The questionnaire evaluated time taken off from work due to hypertension, or to consult a doctor and if the patients were financially penalised for absenteeism from the work place.

(iii) Medical:

The patient's blood pressure was documented from their medical records, if this information was available in the patient's records, in order to establish cost-effectiveness of the antihypertensive drugs. Renal and liver function as well as the potassium, blood glucose, cholesterol and uric acid levels were also recorded from the patient's records. The biochemistry data were recorded in order to determine if any of the antihypertensive drugs were adversely affecting the patients biochemistry (eg. thiazide diuretics may adversely affect blood glucose, potassium levels, cholesterol and uric acid levels) (appendix III).

The patient questionnaire ascertained, by means of spontaneous reporting (open-ended question), if the patient was experiencing any disturbing side effects and if these symptoms influenced compliance with their treatment. The patient was then prompted (close-ended

question) to report on a few of the more important and common side effects of antihypertensive drugs. This part of the questionnaire was adapted and translated from an already tried and validated, self-administered quality of life questionnaire for hypertensive patients. (Bulpitt, C.J. et al; 1990) This questionnaire was found to be suitable for patients on diuretics, beta-blockers, calcium channel blockers, ACE inhibitors and centrally acting drugs.

3.5.3. PRESCRIBER DATA (appendix IV)

Data on the prescribers were obtained from the Register of Medical Practioners issued by the South African Medical and Dental Council and included the year of graduation, the university attended and any other additional qualifications (appendix III).

3.6. SURVEY PROCEDURE

This is a cross-sectional, descriptive study on the use and effects of antihypertensive drugs as they are being used in the Mamre community. Figure 7.3.6. summarises the study design.

STUDY DESIGN

QUALITY ASSURANCE CYCLE

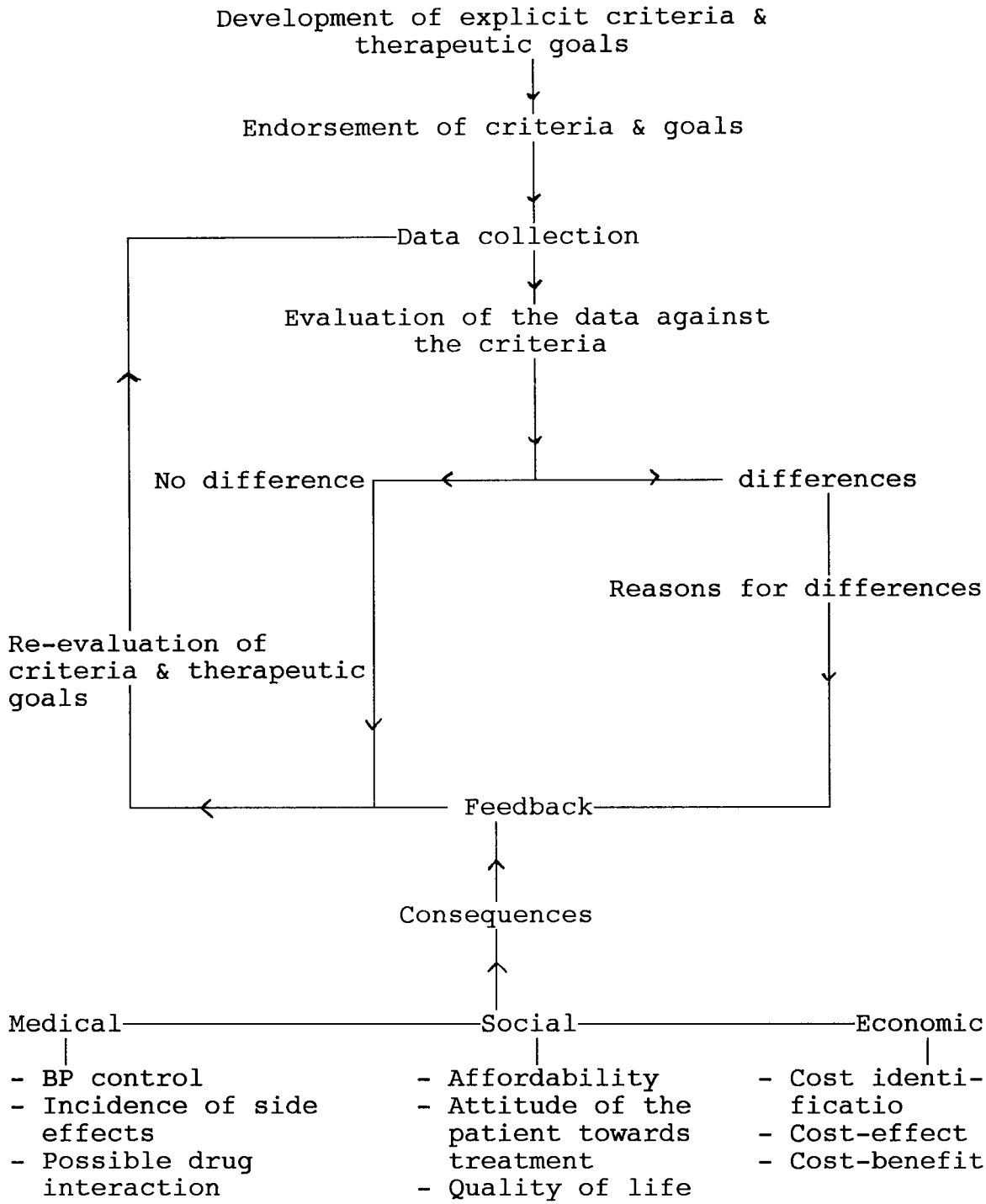

Figure 7.3.6.

Two interviewers visited the study population in their homes. Allocation of respondents was done on a geographical basis rather than by random selection, largely because this technique had been used by previous studies in Mamre.

3.6.1. DEVELOPMENT PHASE

The development phase was completed prior to the commencement of the study. This phase involved:-

(i) the development of a questionnaire, a prescriber data form and a form for recording information from the study participants' medical records, by the researcher.

(ii) the development of explicit criteria by the researcher, in consultation with various specialists in the field and by reviewing the current literature.

(iii) defining therapeutic goals for the treatment of essential hypertension in relation to age, sex and race.

3.6.2. DATA COLLECTION

Data collection was carried out by local fieldworkers, by means of interviews conducted in the respondents home. Data collection commenced on the 1st September 1991 and was completed by November 1991. Interviews usually took place

during the day but participants were visited at night if necessary. The researcher met weekly with the fieldworkers to check for correct completion of the questionnaires. Problems were addressed and if necessary the fieldworker would visit the respondent a second time to clarify their response. Fieldworkers were required to substantiate any missing data. The researcher then collected the data from the patients' records after all the respondents had completed the questionnaire. Data collection from the medical records was completed by April 1992.

3.6.3. EVALUATION AND ANALYSIS PHASE

The questionnaires were marked by the interviewers and then coded by the researcher, according to a set of coding rules drawn up prior to commencement of the analysis. Coding of the data was undertaken simultaneously with the fieldwork to allow for immediate correction of inconsistencies and completion of omissions. The coded data was then analysed at the Department of Biostatistics at the Medical Research Council in Parow, using the SAS^{R} computer package. Variables were initially analysed using simple descriptive statistics. Detailed analysis of all possible data combinations was not attempted. Both parametric and non-parametric tests were used and a p value of less than 0.05 was regarded as statistically significant. The following tests were employed

depending on whether the data were of a continuous or discrete nature:-

(i) Pearson's Correlation Coefficients:

a parametric test for correlation between 2 samples of data.

(ii) Student's - t Test:

a parametric test for significance between 2 independent samples.

(iii) Chi-square Test:

a non-parametric test for association between 2 variables.

(iv) Analysis of Variance:

an analysis of variation among more than 2 independent samples.

3.6.4. FEEDBACK AND RE-EVALUATION OF CRITERIA

The results will be reported to the Mamre Hypertension Group to assist in providing direction for their intervention program which will also involve a report back of the results to the participating doctors and then possible re-evaluation of the criteria.

3.6.5. REASSESSMENT

This phase was not done as part of this study, but will be done as a separate study at the completion of the intervention phase currently being undertaken by the Department of Community Health (UCT), in Mamre.

3.7. CHOICE OF INTERVIEWERS

In setting up the Mamre Community Health Project the Department of Community Health (UCT) together with the Mamre Steering Committee decided that all the fieldworkers used in the studies should be selected from the Mamre community, as they would have the interest of the village at heart and would therefore be highly motivated.

The following criteria were decided upon for the selection of fieldworkers:-

- that they should be unemployed
- that they should be of the same sex
- that they should have at least a standard 8 education
- that they should be approximately 40 years old, as it was considered that this was necessary for questions referring to sexual function.

Two fieldworkers were selected by the Sister-in-charge of the Mamre blood pressure monitoring station.

3.8. TRAINING OF THE FIELDWORKERS

Variability in interviewer technique has been shown to have a great effect on the repeatability of responses, therefore both fieldworkers received training from the MRC. This was a one-day training programme which included the following:-

- background information and understanding of why the study was being conducted
- interviewing techniques
- confidentiality of information
- understanding and familiarity with the questionnaire
- recording of data
- a role-playing of the interview situation
- strategies for dealing with refusals

The researcher participated in this training programme and supervised the data collection.

3.9. PILOT STUDY

A pilot study was undertaken in Mamre as part of the fieldworkers' training program. It also served to test the appropriateness of the questionnaire (i.e. to assess whether it was answerable and the translation to Afrikaans was acceptable and understandable.) A few minor changes were made to the questionnaire at the end of this period in order to assist the fieldworkers in the recording of the data and to improve the clarity of some questions. Both the MRC fieldworker trainer and the researcher were satisfied that the interviewers understood the questionnaire and were consistent with each other.

3.10. ETHICAL CONSIDERATIONS

This study was approved by the Faculty of Medicine's Ethics Committee at the University of Cape Town prior to commencement of the study.

Patients were informed of the details of the study by the fieldworkers and if they freely consented to participate, they were asked to sign their questionnaires. Confidentiality has been ensured by allocating each patient a study number. Confidentiality of the prescribing doctors

was similarly ensured and at no point in the report is any doctor mentioned by name. Permission to access the patient's medical records was obtained from both the patient and the doctor or hospital medical superintendent.

CHAPTER 8 RESULTS

1. Background demographic data

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1.3. Level of schooling

1.4. Employment status

1.5. Chronic medical conditions

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(iv) Blood glucose

(v) Uric acid levels

1. BACKGROUND DEMOGRAPHIC DATA

A total of 247 patients were initially included in the study group. Of these, 41 were found to be no longer on treatment, 5 had left Mamre or could not be traced and 3 had died. Three people refused to participate in the study. The final sample size was 195.

1.1. SEX

Figure 8.1.2.

The selected study sample consisted of 144 (73.8%) females and 51 (26.2%) males.

1.2. AGE

Figure 8.1.2.

The average age of the study population in years was 58.7, with a range of 36 to 85 years. The average age for the women was 59.6 with a range of 36 to 85 years. The median age for the men was 57.8 years, with a range of 37 to 80 years. The mode for both sexes was 60 years.

	Females	Males
Average age (yrs)	59.6	57.8
Range (yrs)	36-85	37-80

TABLE 8.1.2

The average age and age range (in years) of the study population.

1.3. LEVEL OF EDUCATION

Figure 8.1.3.

The average level of education was to standard 5 or standard 6, with 67.7% of the study population having attained this level. Only 11.3% of the participants had a standard 8, 9 or 10 and a further 4.6% had received a tertiary education or trained in a technical skill.

1.4. CHRONIC MEDICAL CONDITIONS

Figure 8.1.4.

The most common chronic medical conditions (apart from hypertension) in the study population were "gout" or rheumatic diseases, diabetes and heart disease. Nineteen percent of the participants reported that they suffered from "gout", 15.9% from diabetes and 13.3% from heart problems.

2. USE OF MEDICAL SERVICES

2.1. MEDICAL FACILITY AT WHICH TREATMENT FOR HYPERTENSION WAS RECEIVED.

Figure 8.2.1.

Analysis revealed that 66.7% (97 females and 33 males) of the study population attend a state facility while the remainder consult with private general practioners. 23.6% (6 males and 40 females) attend more than one medical facility. None of the respondents reported that they consulted alternative healers.

2.2 PRESCRIBER CHARACTERISTICS

Table 8.2.2.

Fifteen different private doctors, in Mamre, Atlantis and Cape Town were consulted by 65 respondents. Two district surgeons (D.S) treated 76 of the respondents and 2 doctors at the Wesfleur day hospital treated 53 respondents, many of whom were also seen by the district nurse at the Mamre district clinic. Nineteen patients were seen by doctors at Woodstock, Somerset and Groote Schuur hospitals.

All but one of the doctors were male and the average number of years in practice for this group was 13 years, with a range of 4 - 37 years. All doctors practising in the Mamre/Atlantis area were fluent in Afrikaans.

	State*	Private
University attended		
Stellenbosch	3	7
Univ. Cape Town	1	4
Orange Free State	0	1
Pretoria	0	1
Outside RSA	0	1
Av. practice years	16.5	12.5
Range (years)	4 - 37	5 - 25
Additional qualifications	0	4

TABLE 8.2.2. Characteristics of the state versus the private sector prescribers.

(* excluding Groote Schuur, Woodstock and Somerset hospitals due to incomplete data)

Figure 8.2.2

Approximately two thirds (67.7%) of the study population did not see the same doctor each time they sought treatment for their hypertension. A comparison between the sexes showed that 56.9% of the men as opposed to 71.5% of the women did not see the same doctor at each visit.

3. USE OF MEDICINES

3.1. DRUGS USED TO TREAT HYPERTENSION

Figures 8.3.1.1. and 8.3.1.2.

Twenty seven different drugs, which could be grouped into 11 pharmacological classes according to the ATC classification (appendix I), were used to treat the study population.

ATC classification	Generic name	Freq	%
Centrally acting	methyldopa	68	25.9
	reserpine	20	7.6
	reserpine co.*	10	3.8
	rauwolfia co.	18	6.8
Alpha-blockers	prazosin	6	2.3
Vasodilators	hydrallazine	3	1.1
Calcium antagonists	nifedipine	1	0.4
	verapamil	5	1.9
	diltiazem	1	0.4
ACE inhibitors	captopril	10	3.8
	enalapril	9	3.4
	lisinopril	1	0.4
	ramipril	1	0.4
Thiazide diuretics	hydrochlothiazide	2	0.8
	cyclopenthiazide	16	6.1
Non-thiazide diuretic	indapamide	16	6.1
Loop diuretic	furosemide	2	0.8
K+ sparring diuretic	spironolactone	2	0.8
	triamterene co.	12	4.6
	amiloride co.	43	16.3
B-blockers;non-selective	propranolol	3	1.1
B-blockers;selective	atenolol	12	4.6
	metoprolol	2	0.8
	TOTAL	263	100.0#

(* reserpine co = Brinerdin^{R}) (# rounded to 100.0%)

TABLE 8.3.1. Drugs used to treat hypertension in the study population.

It was noted that 61.5% (120) of the study population took only one drug for their hypertension, while 33.3% (65) and 5.1% (10) people took 2 and 3 drugs respectively. The drugs most commonly taken together where methyldopa, a reserpine containing agent or a diuretic. Prazosin was the most favoured third line agent.

3.2. DRUG PRESCRIBED VERSUS THE MEDICAL FACILITY

Figure 8.3.2.

ATC classification	Generic name	Private	D.Surg.	Hosp.
Centrally acting	methyldopa	13	31	24
	reserpine	11	9	-
	reserpine co.*	1	5	4
	rauwolfia co.	4	7	7
Alpha-blockers	prazosin	-	1	5
Vasodilators	hydrallazine	1	1	1
Calcium antagonists	nifedipine	1	-	-
	verapamil	-	2	3
	diltiazem	1	-	-
ACE inhibitors	captopril	7	3	-
	enalapril	7	1	1
	lisinopril	1	-	-
	ramipril	1	-	-
Thiazide diuretics	hydrochlothiaz.	1	1	-
	cyclopenthiazide	15	1	-
Non-thiazide diuretic	indapamide	4	11	1
Loop diuretic	furosemide	-	-	2
K+ sparring diuretic	spironolactone	1	1	-
	triamterene co.	3	2	7
	amiloride co.	8	16	19
B-blockers;non-select.	propranolol	2	1	-
B-blockers;selective	atenolol	6	4	2
	metoprolol	1	-	1
	TOTAL	89	97	77

TABLE 8.3.2. Comparison of antihypertensive drugs prescribed by the different medical facilities

3.3. OTHER DRUGS TAKEN

Table 8.3.3.

A total of 60 different drugs, other than antihypertensives, were taken by 42.6% (83) of the study population. Twenty-nine (15%) people took one drug, 38 (19.5%) people took 2 drugs, 13 (6.7%) took 3 drugs and 3 (1.5%) people took 4 different other drugs.

The following 10 drugs were the most commonly prescribed. The other 50 drugs were only prescribed once.

Drug name	Freq. of use
Indomethacin	20
Glibenclamide	17
Drug unknown	11
Metformin	9
Isosorbide dinit subl.	7
Isosorbide dinit 40mg	5
Diclophenac	5
Digoxin	5
Insulin	4
Benzodiazepines	4
TOTAL	87

TABLE 8.3.3. The most commonly used other drugs.

4. SOCIAL CONSEQUENCES

Social consequences were estimated according to the respondents' rating of their perception of the quality of the medical service they received, their perceived health on antihypertensive treatment, by estimating the patients' compliance with their treatment and evaluating their perceived quality of life.

4.1. ATTITUDE TOWARDS THE MEDICAL SERVICE RECEIVED.

Figure 8.4.1.

When asked how they rate the medical service they receive, 88.2% of the participants rated it to be either excellent or good and only 3.1% considered the service to be poor or useless.

4.2. PATIENTS PERCEPTION OF THEIR HEALTH ON ANTI-HYPERTENSIVE TREATMENT.

One hundred and sixty-six (85%) of the study population claimed that they felt better since starting their treatment for hypertension, while 29 (15%) said they felt no difference. None of the respondents claimed that the treatment made them feel worse.

4.3. ESTIMATED COMPLIANCE WITH ANTIHYPERTENSIVE DRUGS

Figure 8.4.3.

The participants in the study were considered to be compliant with their drug treatment 62.1% of the time and probably compliant 9.0% of the time. Noncompliance for the group was estimated to be 15.8% and probable non compliance 13.1%. Due to records for some patients being unavailable, 72 (27.4%) of the antihypertensive drugs used could not be evaluated.

4.4. QUALITY OF LIFE

Figure 8.4.4.

Normal daily activities were still being performed by 84% (n=163) of the study participants, 7% (n=14) could perform their daily tasks with effort, 4% (n=8) with assistance and 5% (n=10) were incapacitated. Participants not able to continue with their normal daily activities complained of tiredness, general malaise, "gout" and 6 participants were debilitated as a result of heart attacks.

The question on whether antihypertensive drugs or hypertension interferes with the study participants' leisure time was not analysed due to poor understanding of the question by the participants, which resulted in interviewer prompting.

5. ECONOMIC CONSEQUENCES

5.1. EMPLOYMENT STATUS

Figure 8.5.1. and Figure 8.5.1.2

Only 24% (n=46) of the study population were in paid employment, 38% (n=77) were pensioners, 7% (n=14) received a state medical grant, 28% (n=55) worked but were not paid for their work and just 2% (n=3) were noted to be unemployed. Forty five percent (n=23) of the men and 16% (n=23) of the women were in paid employment, while 37% (n=53) of the women and 4% (n=2) of the men were working but not being paid.

5.2. RESPONSIBILITY FOR PAYMENT

Figure 8.5.2.

The state pays or subsidises 36% (n=69) of the participants' medical treatment for hypertension, the medical schemes 21% (n=40), the employer 2% (n=4) and 40% (n=78) of the study participants were responsible for paying for their own treatment. Of those participants who were on medical aid, 39 (97.5%) consulted a private doctor.

5.3. AFFORDABILITY OF THE MEDICINES

Figure 8.5.2.

Of the 78 respondents who had to pay for their medical treatment themselves, 32 (41%) said they could afford it, while 41 (53%) could not. Five (6%) of the respondents claimed that they could sometimes afford their medical treatment.

Patients who had to pay for their own consultations and medicines, whether they could afford it or not, paid significantly more than those for whom the medical aids paid or the state paid ($p= <0.001$). While the respondents' ability or inability to pay for their antihypertensive drugs did not significantly influence how much they paid each month for their medicines ($p= 0.100$).

5.4. COST OF A DOCTORS VISIT

Table 8.5.4.

The cost, to the patient, for a visit to the doctor ranged from no cost (R0.00) to R95.00. The mean cost for the study population was R5.11 (standard deviation 11.07), while the mode and median were R0.00.

There was a statistically significant association (p= < 0.001) between how much patients paid to see a doctor (in rands) and the nature of the medical facility where the people sought medical care. If the patient paid for their own medicines then on average the most was paid by those who went to a day or teaching hospital, then a private doctor and the least was paid by patients who attended the district surgeon.

	District surgeon	Private doctor	Hospital Dr.
Range	R0.00 - 30.00	R 0.00 - 95.00	R0.00 - 21.00
Mean	R1.04	R 9.14	R5.80
Median	R0.00	R 0.00	R5.00
Mode	R0.00	R 0.00	R5.00
Std. dev	4.40	17.40	3.24

TABLE 8.5.4. Doctor's fee according to the medical facility.

5.5. COST OF ANTIHYPERTENSIVE DRUGS

Table 8.5.5.

The cost of antihypertensive drugs to the payer ranged from a negligable amount (ie. less than R1.00) to R394.00. The mean cost was R25.91 (standard deviation 48.95), while the median was R8.00 and the mode was R5.00.

Who accepts payment for medical treatment also significantly influences the amount of money paid for medicines each month (p= < 0.001). Medical aids pay the most for medicines, then patients who pay for their own medicines and the state pays the least.

	District surgeon	Private doctor	Hospital Dr.
Range	R0.00 - 11.00	R 0.00 - 394.00	R 0.00 - 45.00
Mean	R4.50	R62.89	R10.90
Median	R4.00	R41.00	R 8.00
Mode	R5.00	R10.00	R 8.00
Std. dev.	2.91	69.92	10.76

TABLE 8.5.5. The cost of hypertension treatment in relation to the medical facility used.

5.6 ABSENTEEISM FROM WORK

Tables 8.5.6.1. and 8.5.6.2.

Of the 46 participants in full time paid employment, 91.3% (n=42) had not been absent from work during the last month due to their hypertension, 1 women and 1 man were absent for 2 days and 2 women had been absent for 3 working days in the last month. Participants took between 0 and 8 hours off work each month to consult a doctor for hypertension management. The mean time taken off work was 2,5 hours, but the mode was 0 hours. All participants received their full salary despite absenteeism from work.

Days off	Females	Males	Total	%
0 days	20	22	42	91.3
1 day	0	0	0	0.0
2 days	1	1	2	4.3
3 days	2	0	2	4.3
TOTAL	23	23	46	100.0#

(# rounded to 100.0%)

TABLE 8.5.6.1. Days off work due to hypertension

Hours off	Females	Males	Total	%
0 hours	14	12	26	56.4
2 hours	1	0	1	2.2
3 hours	1	0	1	2.2
4 hours	1	7	8	17.4
6 hours	1	0	1	2.2
8 hours	5	4	9	19.6
TOTAL	23	23	46	100.00

TABLE 8.5.6.2 Hours off work to consult a doctor for hypertension management

6. MEDICAL CONSEQUENCES

6.1. APPROPRIATE USE OF ANTIHYPERTENSIVE DRUGS.

Figure 8.6.1.

A total of 267 scripts for antihypertensive drugs were issued. Use of these drugs was found to be correct 187 (70%) times, when judged against predetermined criteria (appendix V). Eleven (4%) of the drugs were excluded from evaluation due to inaccurate information from the respondent. Incorrect use was divided into the following sub-groups:-

(i) not appropriate for the management of hypertension (6% ; n = 4)

(ii) dose too high (71% ; n = 49)

(iii) combination product used (23% ; n = 16).

6.2. SIDE EFFECTS OF ANTIHYPERTENSIVE TREATMENT

(i) OCCURRENCE OF SIDE EFFECTS

Figure 8.6.2.1.

Spontaneous reporting of side effects was higher for the women than for the men; 50% (n=69) of the women as opposed to 23.5% (n=12) of the men volunteered that they experienced side effects, which they attributed to their antihypertensive drug treatment.

Of the total study population, 41.5% (n=81), reported experiencing side effects with the antihypertensive drugs.

(ii) a. SIDE EFFECTS EXPERIENCED

Figure 8.6.2.2.

The most commonly experienced side effect was that of tiredness (49%). Thirty one percent of those interviewed claimed to experience side effects only if they forgot to take their pills. Of the 81 people who experienced side effects, 5 decided to stop taking the drug, 8 made a modification to the prescribed treatment regimen and took their tablets only now and again, while the remaining 68 respondents continued to take their tablets as prescribed.

(ii) b. SPECIFIC SIDE EFFECTS EXPERIENCED ON QUESTIONING

Figure 8.6.2.3.

When questioned about specific side effects which have been associated with the use of antihypertensive drugs, it was noted that the most commonly occurring effects where those of blurred vision (48%), leg cramps (43%), headache (39%) and the diuretic effect (34%).

Side effect	Freq.	%
Blurred vision	94	48
Leg cramps	83	43
Headache	76	39
Diuretic effect	67	34
Hot flushes	65	33
Sleepy	64	33
Lightheaded	62	32
Dry mouth	53	27
Constipated	49	25
Dry cough	39	20
Cold fingers	31	16
Bad dreams	29	15
Blocked nose	26	13

TABLE 8.6.2.3 Occurrence of specific side effects

The question relating to the impact of the drugs on sexual function was not answered by 17 study participants and 140 participants reported that they were no longer sexually active. Of the remaining 38 participants (20 females and 18 males) 21 reported they had less interest in sex. The male respondents were asked about specific side effects relating to sexual function. Of the 51 male respondents, 18 were still sexually active and 10 of these men stated that they had problems in sustaining an erection and/or were troubled with failure to ejaculate during sexual intercourse.

(ii) c. SIDE EFFECTS IN RELATION TO ANTIHYPERTENSIVE DRUGS

Due to the relatively small sample sizes for the different types of antihypertensive drugs, only the following drugs were analysed, using the chi-squared test, against specific side effects :-

methyldopa (n=68),

potassium sparing diuretics (n=57),

reserpine containing drugs (n=48) and

ACE inhibitors (n=21).

The only statistically significant association was between ACE inhibitors and the effect of blurred vision (χ^2 = 0.005).

6.3. BLOOD PRESSURE CONTROL

The blood pressure of 43 participants could not be recorded as no medical records for these patients were available.

6.3.1. SYSTOLIC BLOOD PRESSURE

Figure 8.6.3.1.

73% of the study participants were noted to have recorded blood pressures of less than 160mmHg, 7.5% had a reading of 160-169mmHg and 19.5% had systolic blood pressures of greater than 170mmHg.

6.3.2. DIASTOLIC BLOOD PRESSURE

Figure 8.6.3.2.

A diastolic blood pressure of less than 95mmHg was recorded for 66.3% of the participants, a level of 95-99mmHg for 4.6% and 29.1% were noted to have a diastolic pressure greater than 100mmHg.

6.3.3 BLOOD PRESSURE CONTROL IN RELATION TO THE ANTIHYPERTENSIVE DRUG USED

Table 8.6.3.

Blood pressure control (less than or equal to 160/95mmHg) was statistically significantly related to the use of methyldopa and poor control was associated with reserpine and ACE inhibitors.

DRUG	CONTROL <160/95	>160/95	NO. OF READINGS VALIDATED	MISSING DATA	x^2
Methyldopa	34	16	50	18	0.031
K^+ sparing	23	20	43	12	0.738
Non thiazide	7	8	15	1	0.462
Rauwolfia co.	10	5	15	3	0.365
Reserpine	4	10	14	6	-0.032
Reserpine co.	6	3	9	1	0.492
ACE inhibitor	5	14	19	2	-0.006
Atenolol	4	4	8	4	0.742

TABLE 8.6.3.3 Antihypertensives in relation to blood pressure control

6.3.4. BLOOD PRESSURE CONTROL IN RELATION TO THE MEDICAL FACILITY ATTENDED

Table 8.6.3.4

A blood pressure of greater than or equal to 160/95 was classified as not controlled. Nearly fifty percent (45.6%) of the participants blood pressure was controlled. Participants attending the state hospitals had the highest incidence of control (57.4%), while those that attended a private doctor were least controlled (33.8%).

	Dist.surgeon Freq (%)	Hospital Freq (%)	Private Freq (%)	Total Freq (%)
<160/95	36 (47.4)	31 (57.4)	22 (33.8)	89 (45.6)
>160/95	24 (31.6)	15 (27.8)	24 (36.9)	63 (32.3)
not recorded	16 (21.0)	8 (14.8)	19 (29.2)	43 (22.1)
TOTAL	76 (100.0)	54 (100.0)	65# (100.0)	195 (100.0)

(# rounded to 100.0%)

TABLE 8.6.3.4 Blood pressure control according to the medical facility attended by the participant.

6.4. DRUG INTERACTIONS

Table 8.6.4.

Eighty eight (45.1%) of the study participants used one drug. In the remaining 107 participants, there was a theoretical risk of 39 possible interactions occurring, where more than one drug was taken for hypertension or drugs were taken for other conditions. This incidence gives a probability that 1 patient in every 2 - 3 is at risk of experiencing a drug interaction, if more than one drug is taken. The possible interactions were divided into the following sub-groups :-

Type of interaction	Frequency (%)
Major interactions	0 (0.0)
Moderate interactions	11 (28.2)
Minor interactions	17 (43.6)
Side effects exacerbated	11 (28.2)
Total	39(100.00)

TABLE 8.6.4. Interactions between all the drugs.

(appenddix I (5))

6.5. BIOCHEMISTRY RESULTS

(i) Renal function

Renal function	Female	Male	Total
Normal	2	1	3
Mild renal failure	0	1	1
Moderate renal failure	1	1	2
Not recorded	141	48	189

TABLE 8.6.5.1 Renal function recorded from the respondents' medical records.

(ii) Liver function

Liver function	Female	Male	Total
Normal enzymes	0	1	1
Raised enzymes	1	1	2
Not recorded	143	49	192

TABLE 8.6.5.2. Liver functions recorded from the respondents medical records.

(iii)Potassium level

Potassium level	Female	Male	Total
Normal	2	2	4
High	0	0	0
Low	2	0	2
Not recorded	140	49	189

TABLE 8.6.5.3. Potassium levels recorded from the respondents medical records.

(iv) Total Cholesterol

Total Cholesterol	Female	Male	Total
Normal range	7	2	9
High	1	0	1
Low	1	1	2
Not recorded	135	48	183

TABLE 8.6.5.4. Total cholesterol levels recorded from the respondents medical records.

(v) Blood glucose

Blood glucose	Female	Male	Total
Normal range	35	15	50
Raised	31	7	38
Not recorded	78	29	107

TABLE 8.6.5.5. Blood glucose levels recorded from the respondents medical records.

(vi) Uric acid levels

Uric acid	Female	Male	Total
Normal	0	0	0
Raised	1	1	2
Not recorded	143	50	193

TABLE 8.6.5.6. Uric acid levels recorded from the respondents medical records.

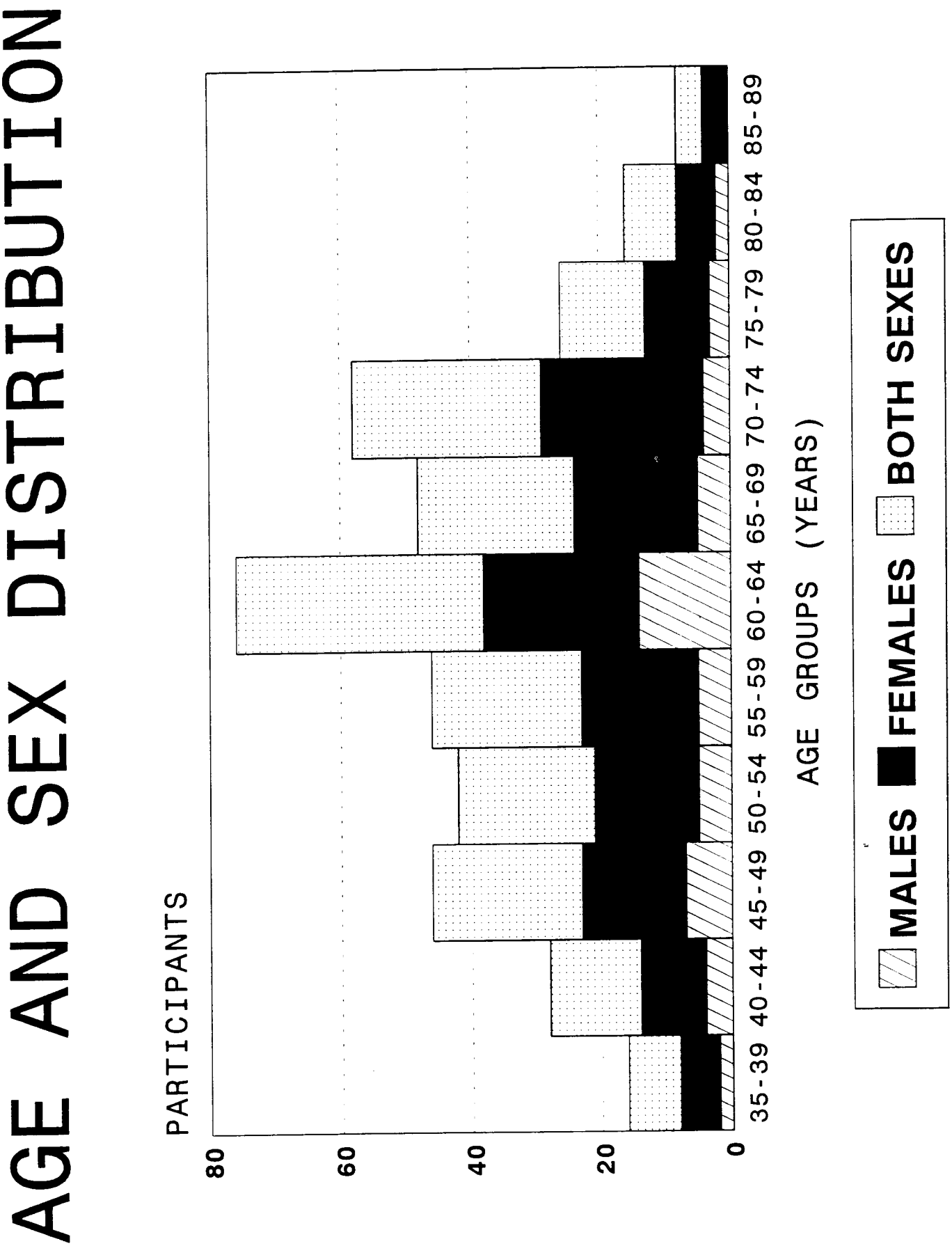
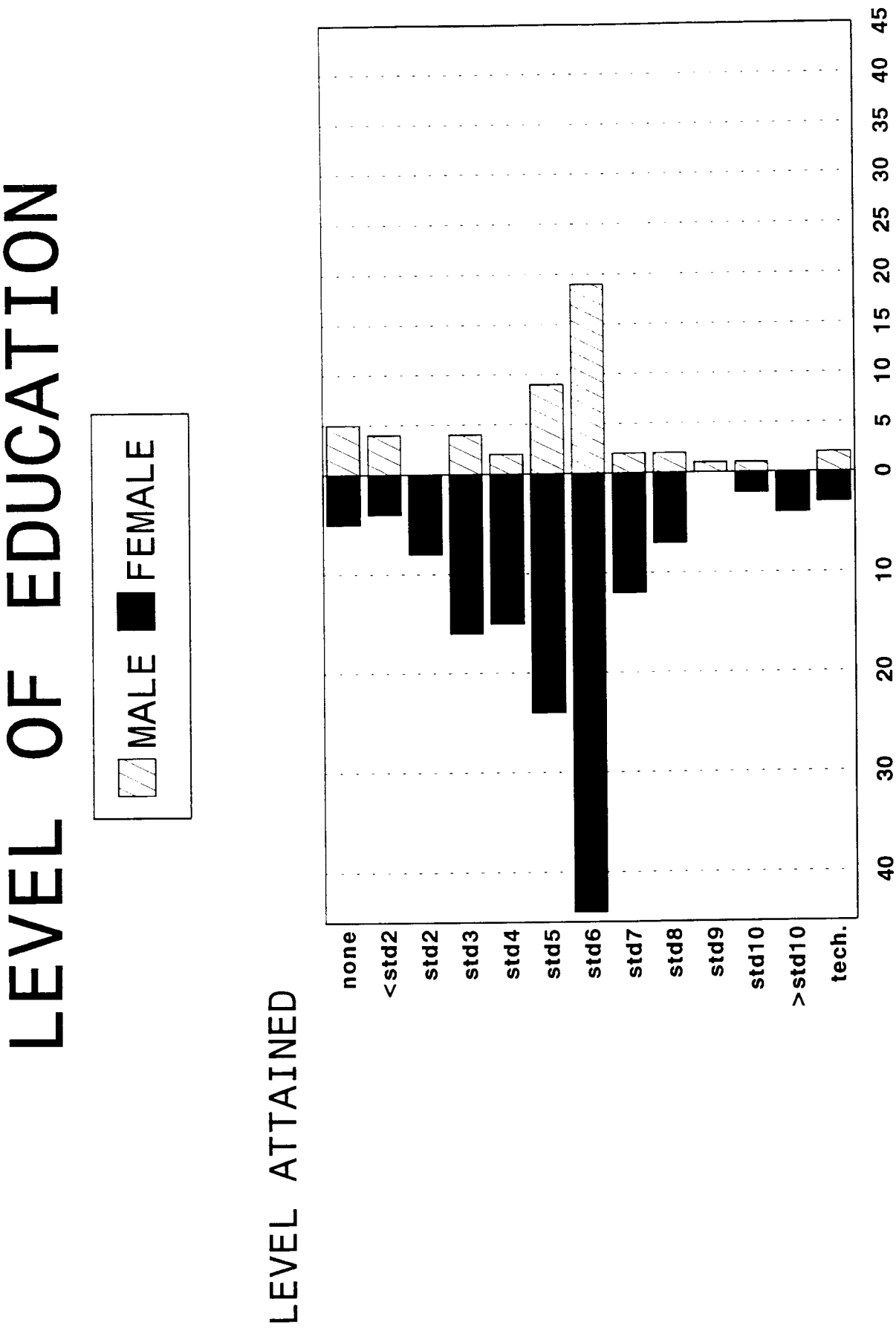

AGE AND SEX DISTRIBUTION
PARTICIPANTS
80
60
40
20
0
35-39 40-44 45-49 50-54 55-59 60-64 65-69 70-74 75-79 80-84 85-89
AGE GROUPS (YEARS)
MALES
FEMALES
BOTH SEXES

Figure 8.1.2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FEMALE
LEVEL ATTAINED
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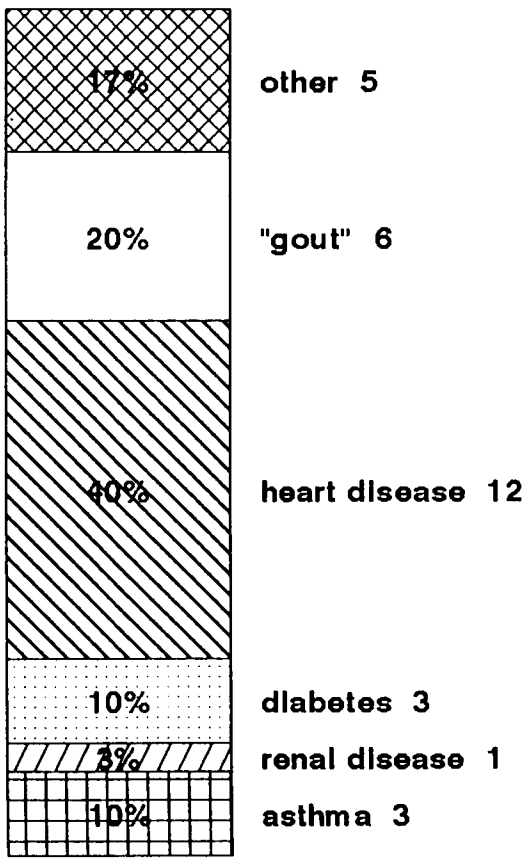
std5
std6
std7
std8
std9
std10
>std10
tech.
40 30 20 10 0 5 10 15 20 25 30 35 40 45
PARTICIPANTS

Figure 8.1.3

CHRONIC MEDICAL CONDITIONS



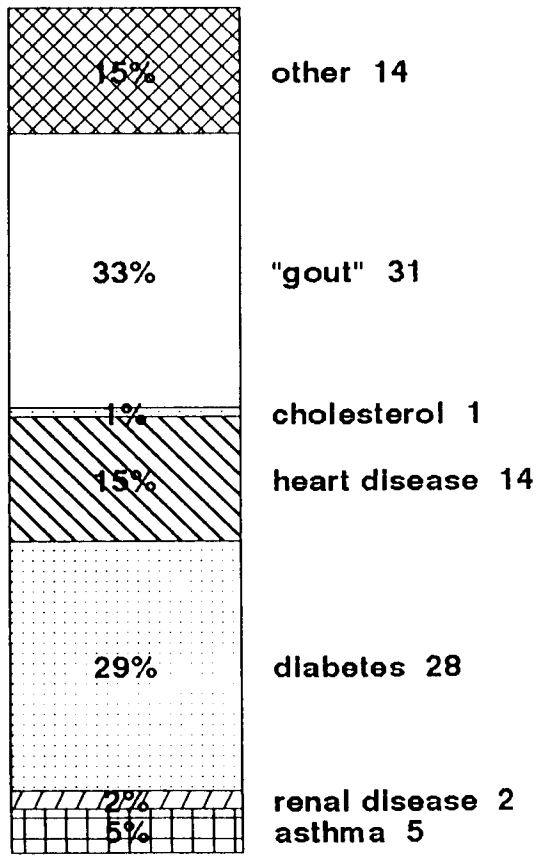


Figure 8.1.4

USE OF MEDICAL SERVICES

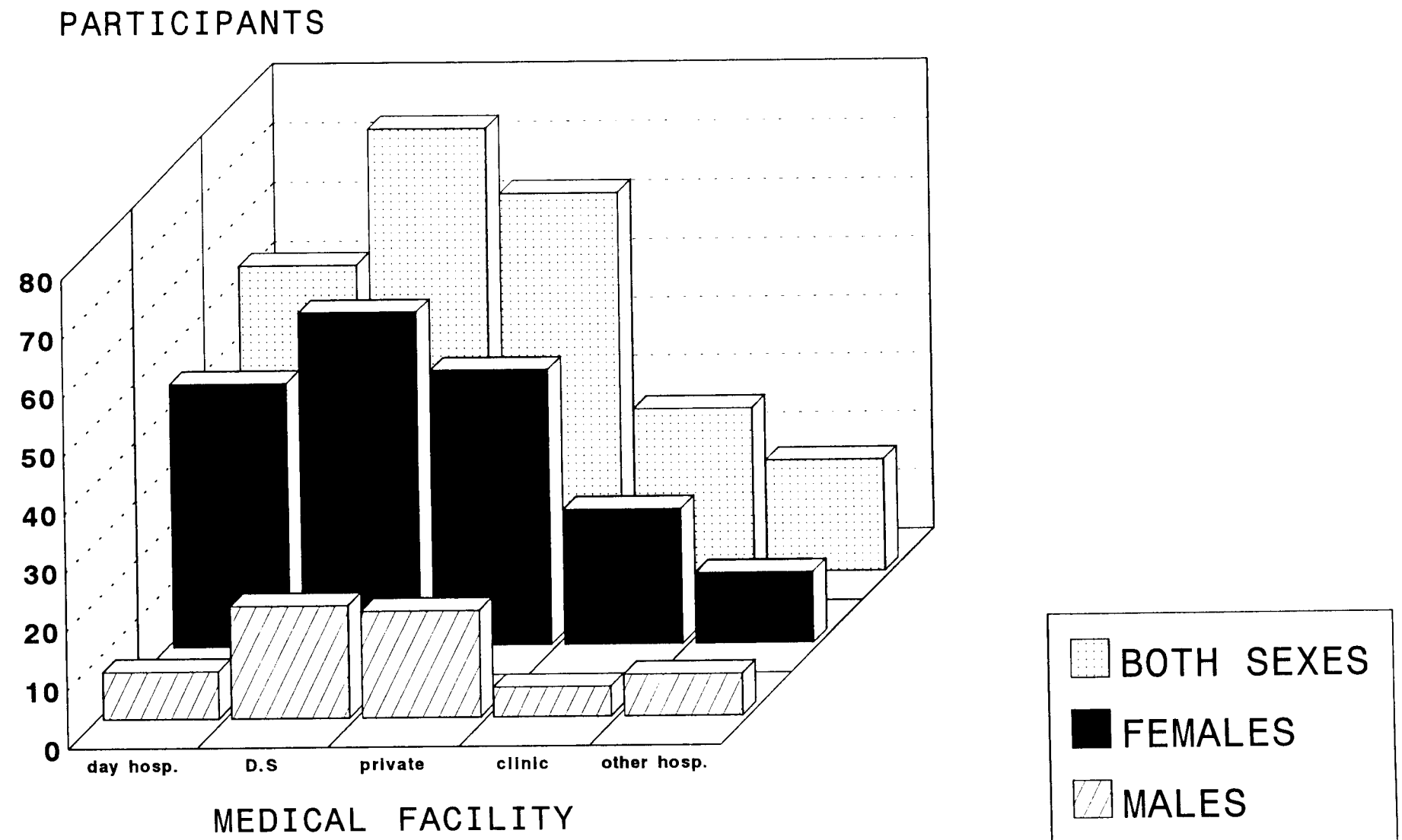


Figure 8.2.1

USE OF MEDICAL SERVICES

ATTENDANCE TO THE SAME DOCTOR

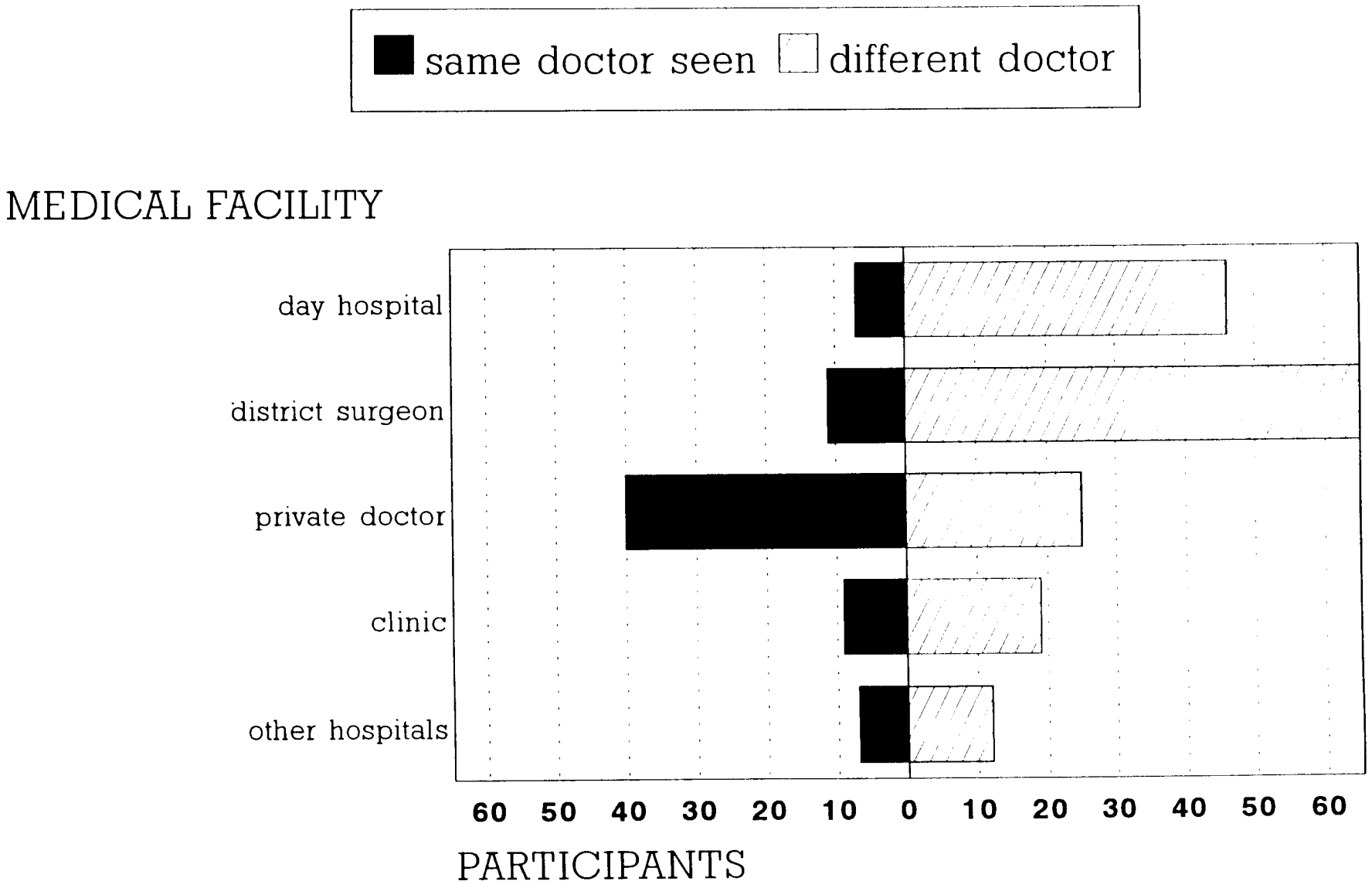


Figure 8.2.2

ANTIHYPERTENSIVE DRUGS USED

TOP 12 ACCORDING TO GENERIC NAME

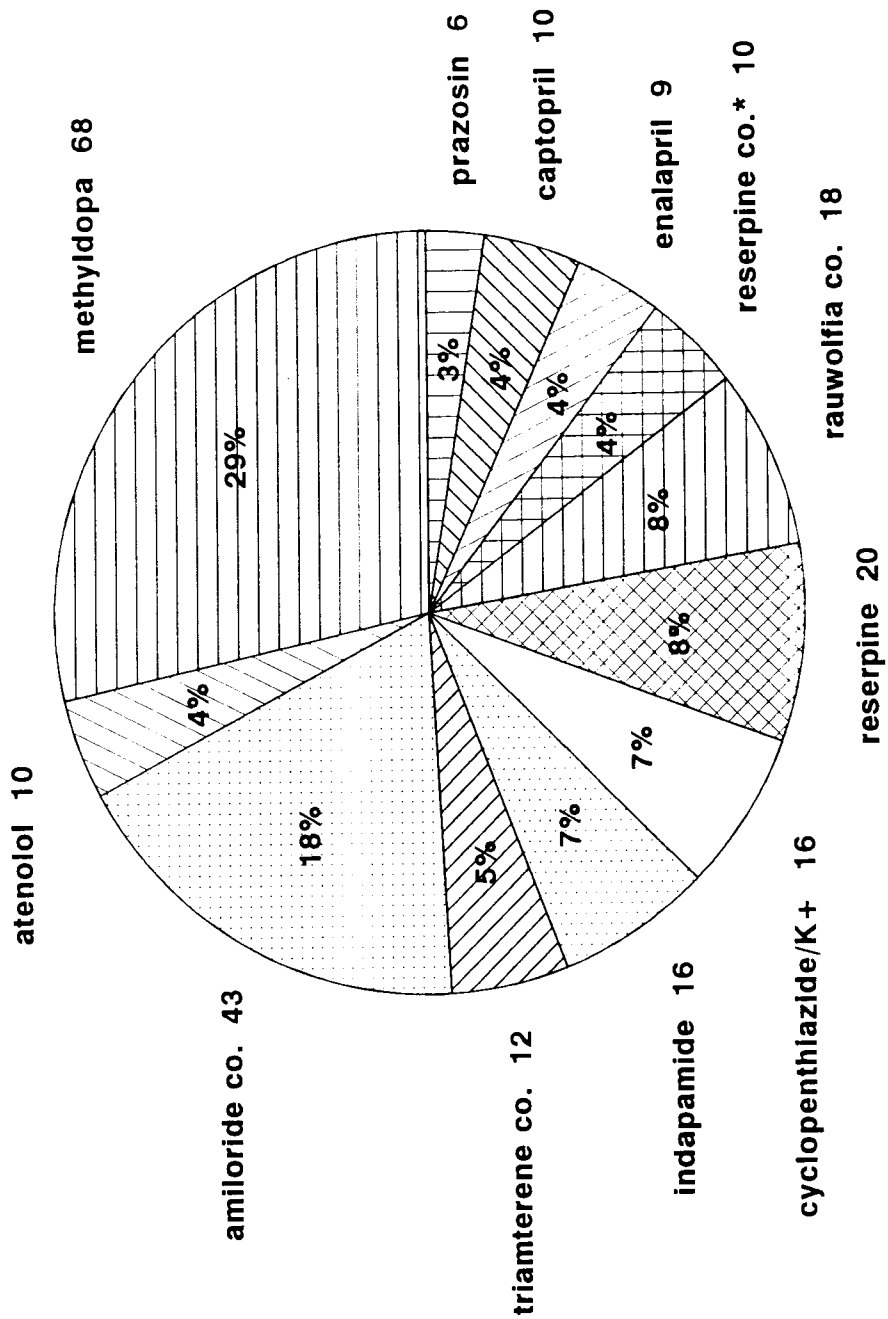


Figure 8.3.1.2

ANTIHYPERTENSIVE DRUGS USED
GROUPED ACCORDING TO ATC CLASSIFICATION

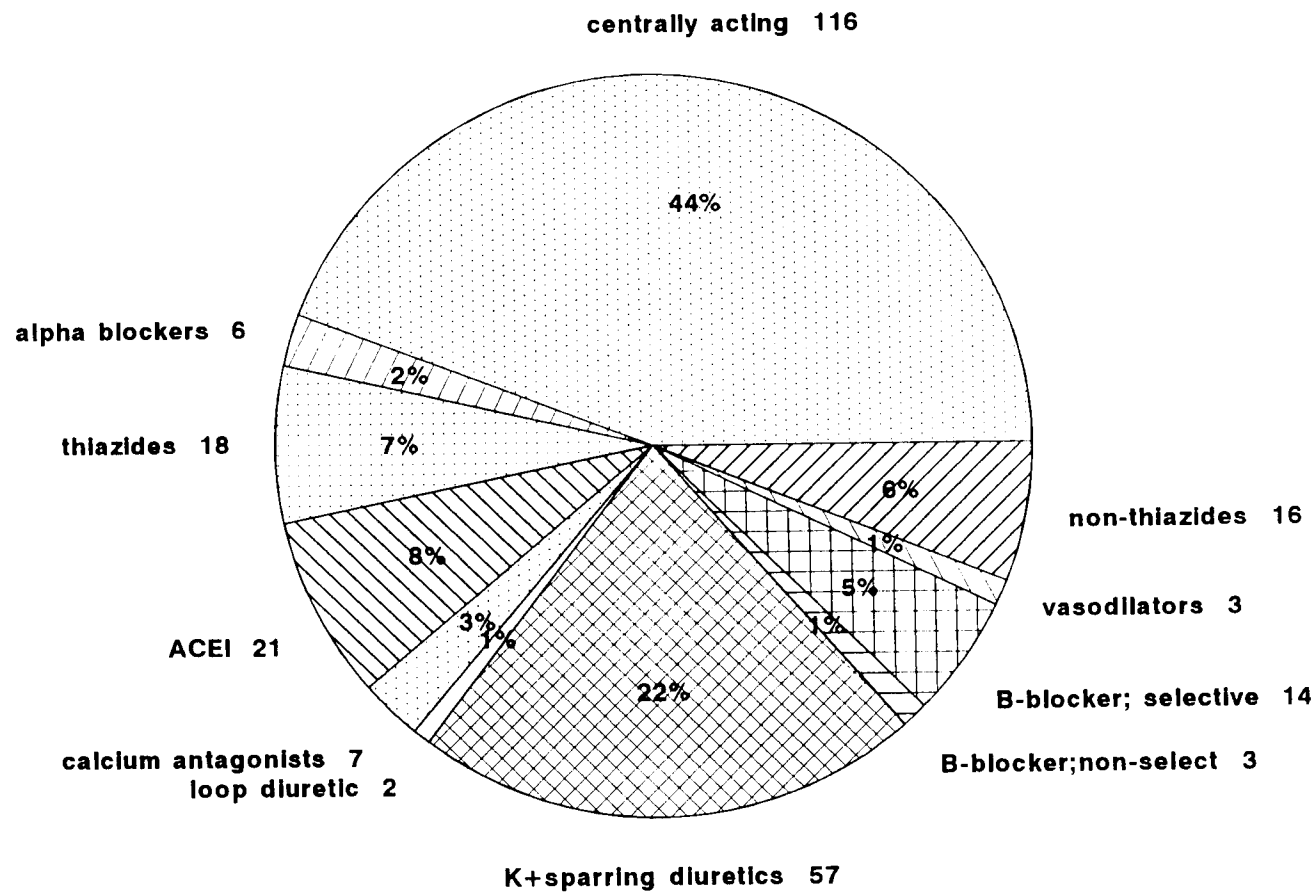


Figure 8.3.1.1

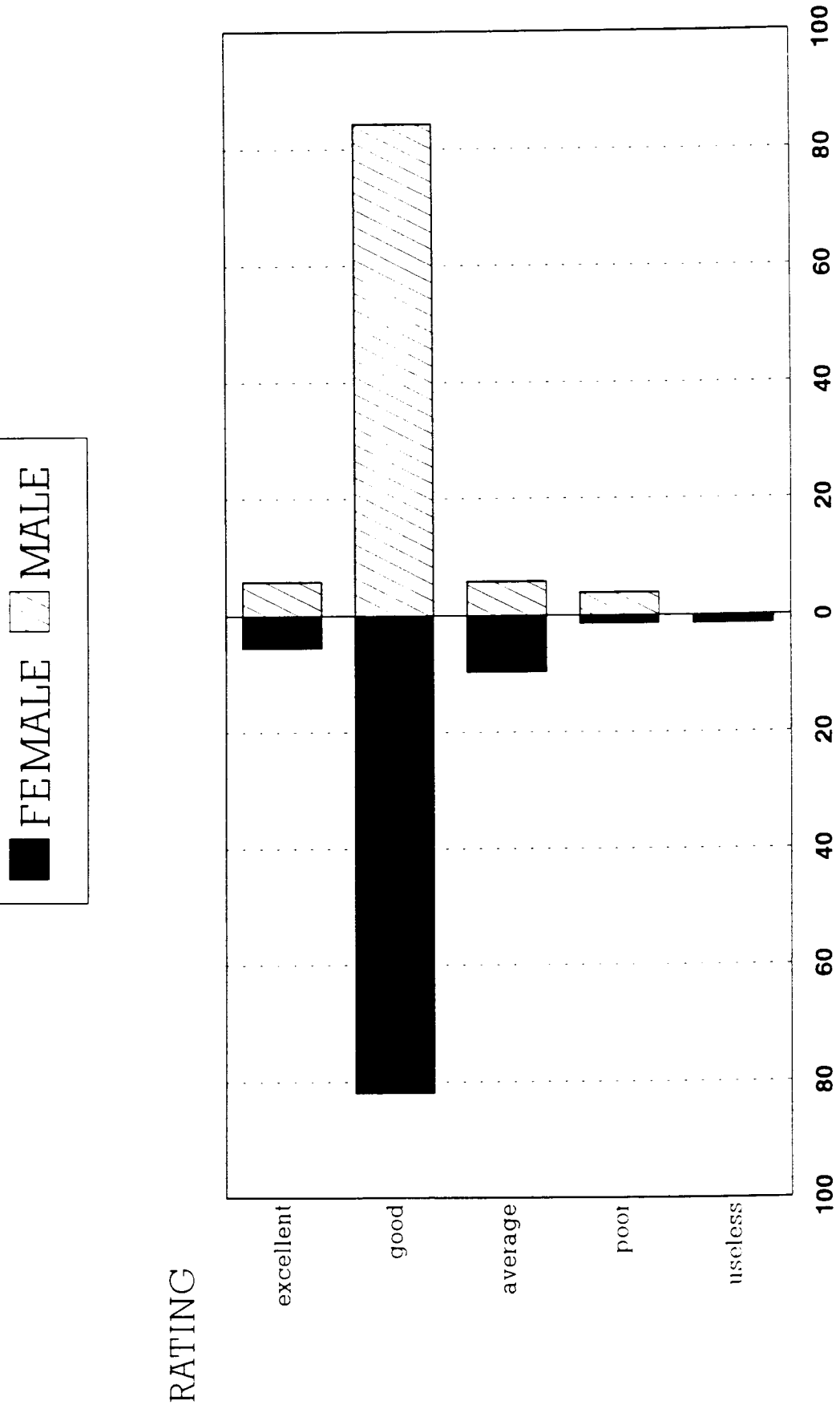
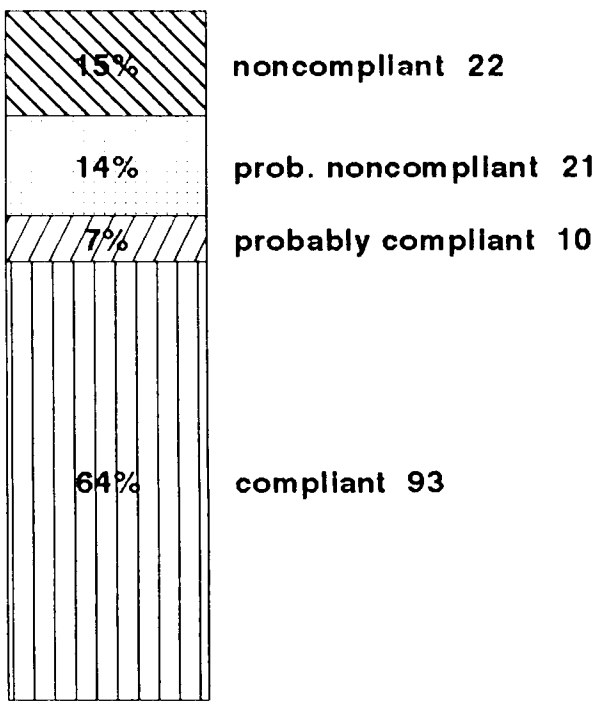

SOCIAL CONSEQUENCES
ATTITUDE TOWARDS MEDICAL SERVICE
FEMALE
MALE
RATING
excellent
good
average
poor
useless
100
80
60
40
20
0
20
40
60
80
100
PARTICIPANTS %

Figure 8.4.1

SOCIAL CONSEQUENCES

ESTIMATED COMPLIANCE



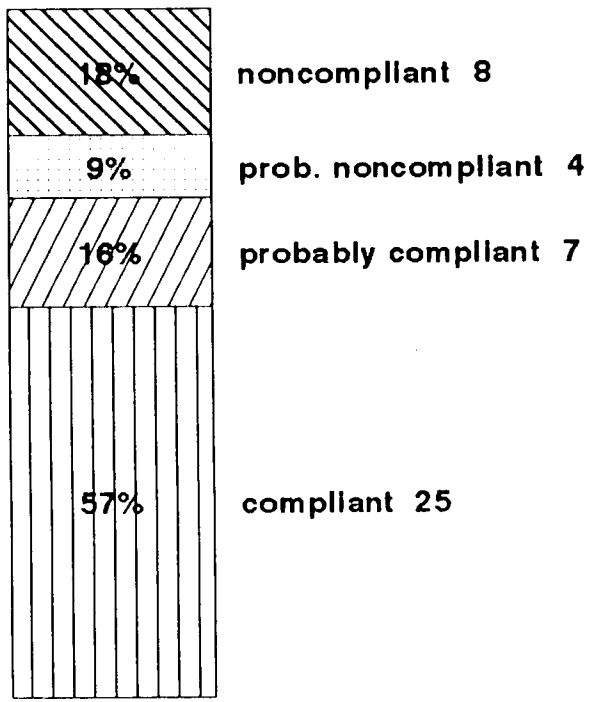


Figure 8.4.3

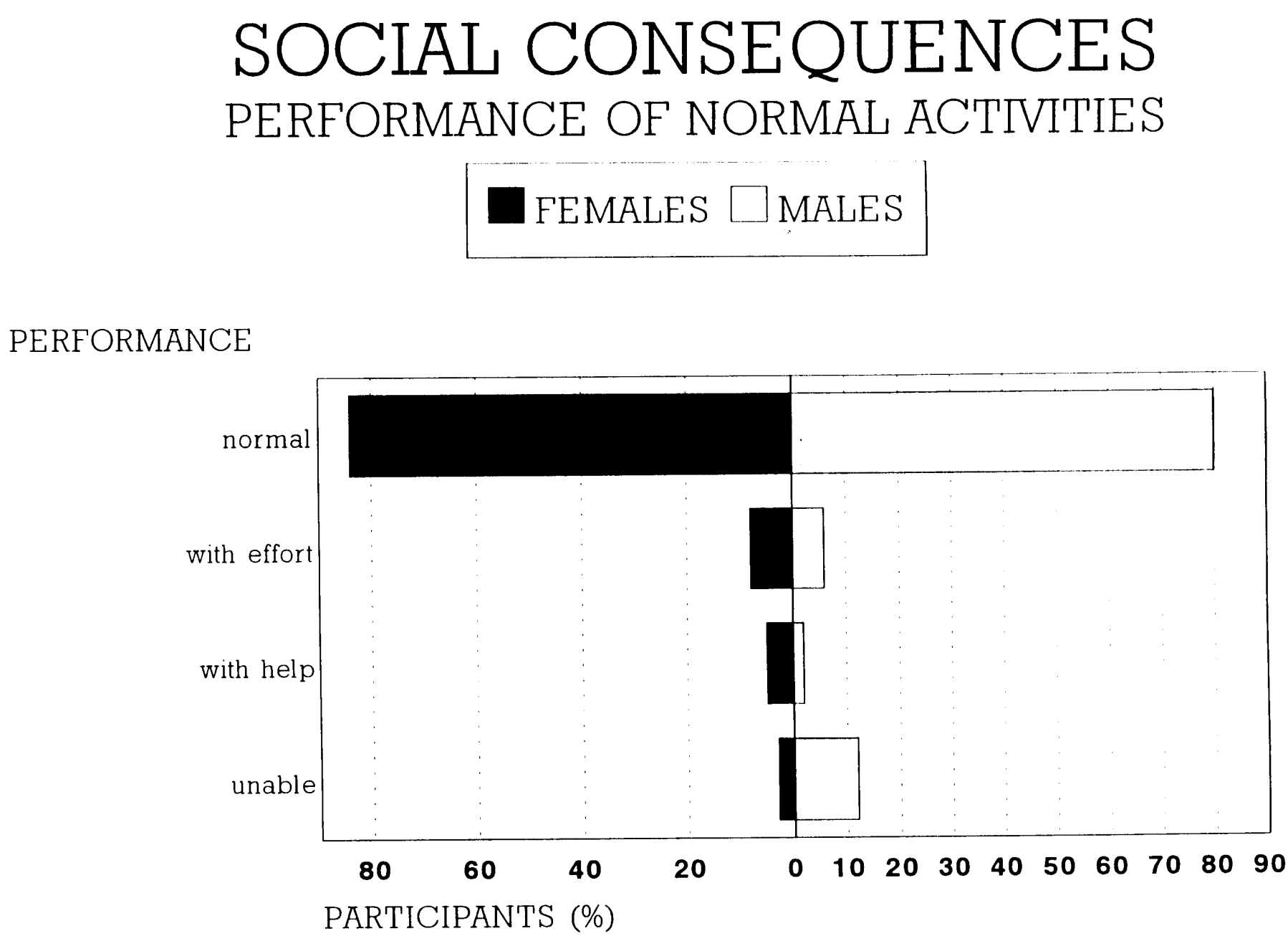

SOCIAL CONSEQUENCES
PERFORMANCE OF NORMAL ACTIVITIES
FEMALES
MALES
PERFORMANCE
normal
with effort
with help
unable
80
60
40
20
0
10
20
30
40
50
60
70
80
90
PARTICIPANTS (%)

Figure 8.4.4.

ECONOMIC CONSEQUENCES

EMPLOYMENT STATUS OF PARTICIPANTS

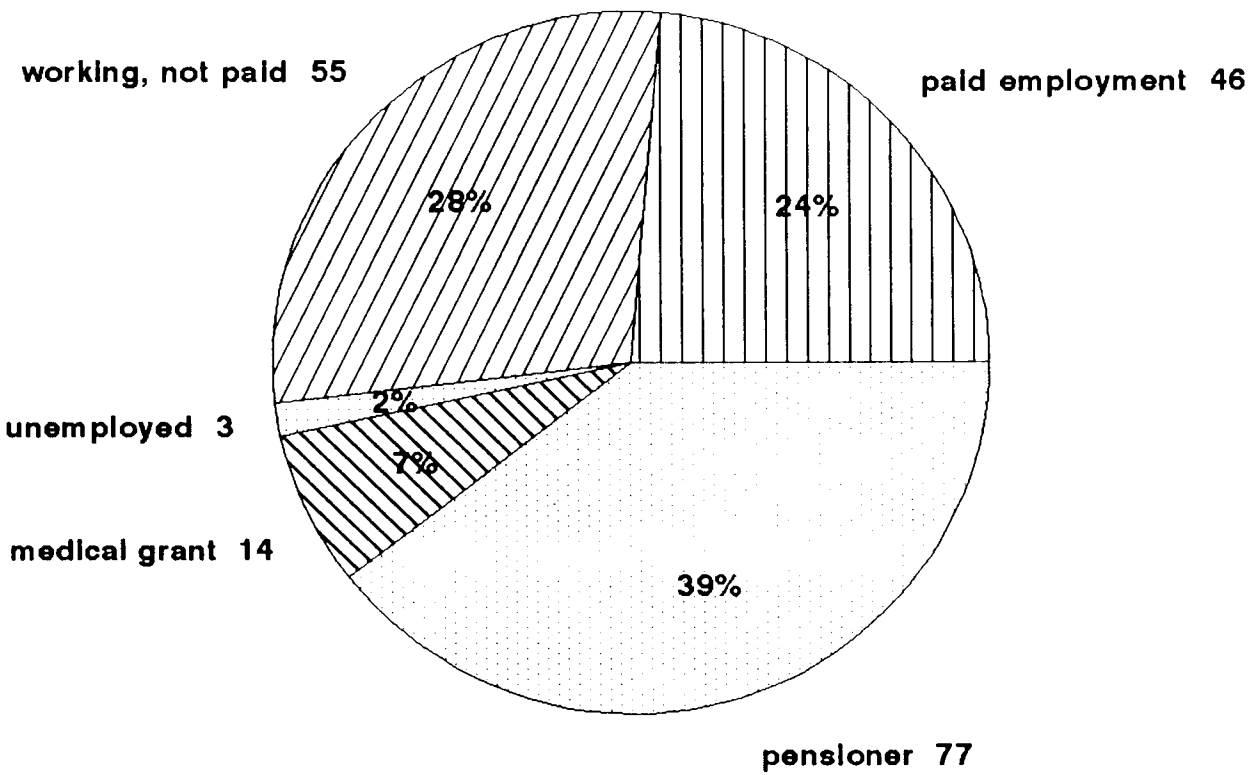


Figure 8.5.1.1

ECONOMIC CONSEQUENCES

EMPLOYMENT STATUS ACCORDING TO SEX

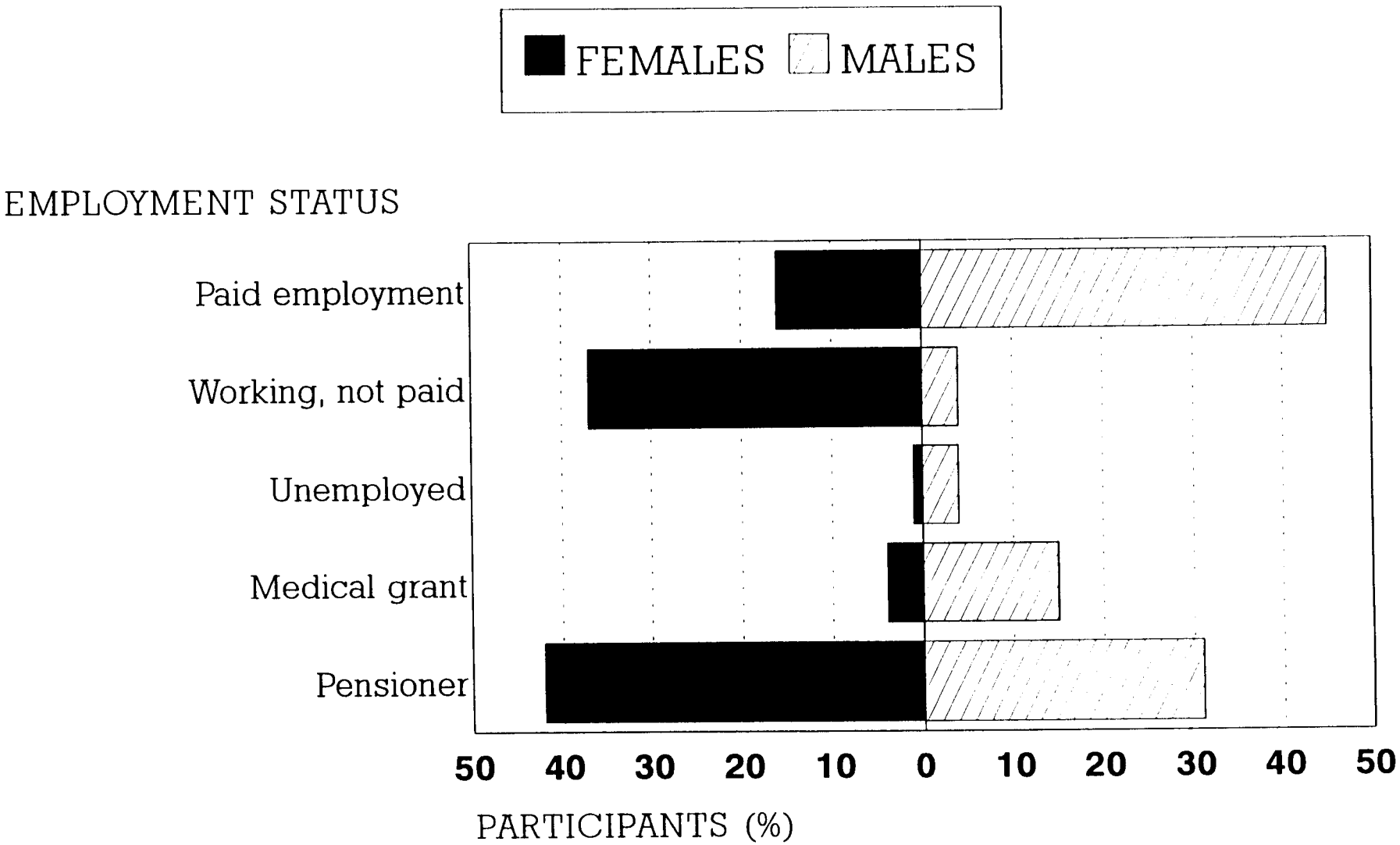


Figure 8.5.1.2

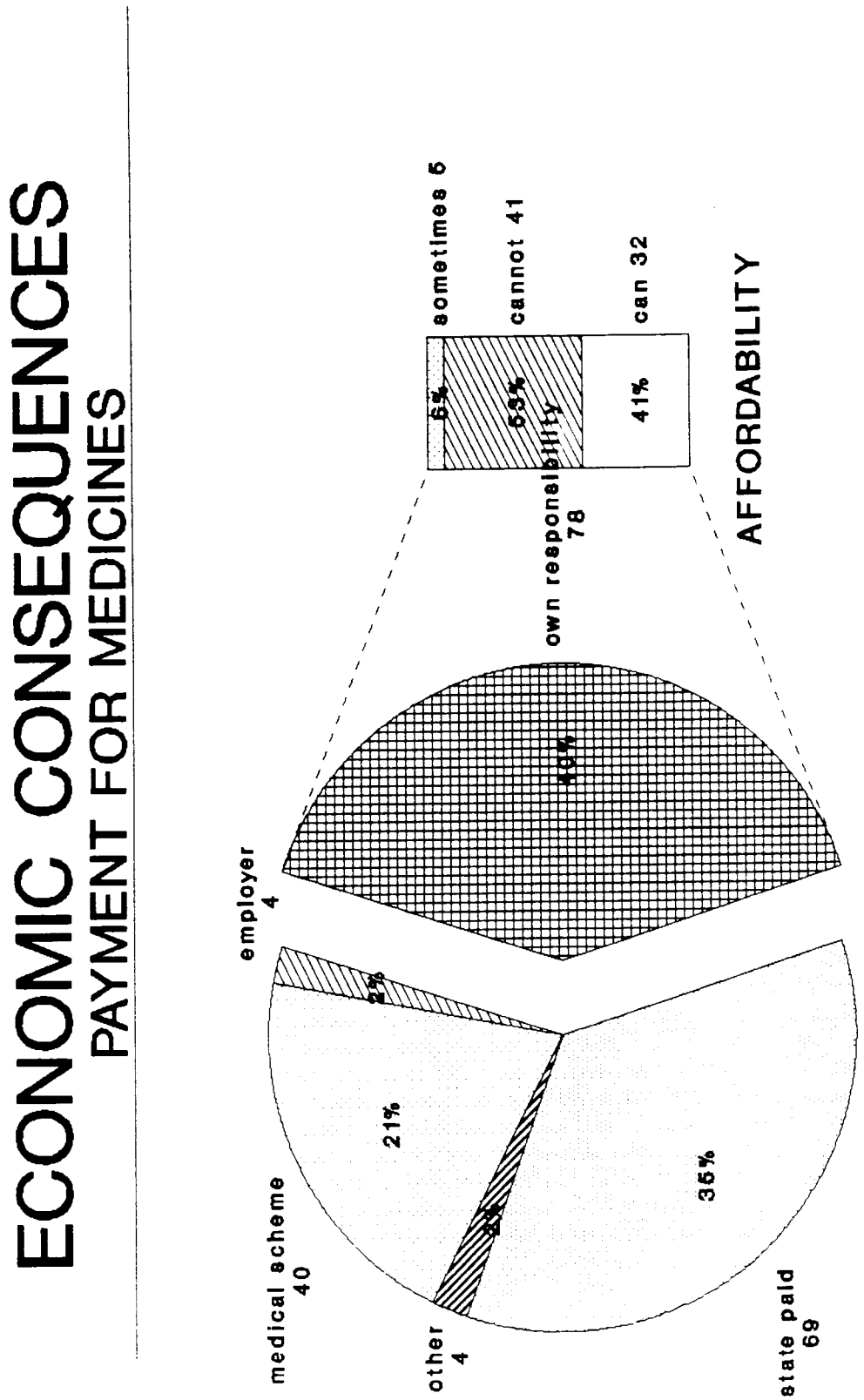

ECONOMIC CONSEQUENCES
PAYMENT FOR MEDICINES
AFFORDABILITY
RESPONSIBILITY
sometimes 6
cannot 41
can 32
6%
53%
41%
own responsibility
78
employer
4
40%
medical scheme
40
21%
2%
other
4
4%
state paid
69
35%

Figure 8.6.2

MEDICAL CONSEQUENCES

APPROPRIATE USE

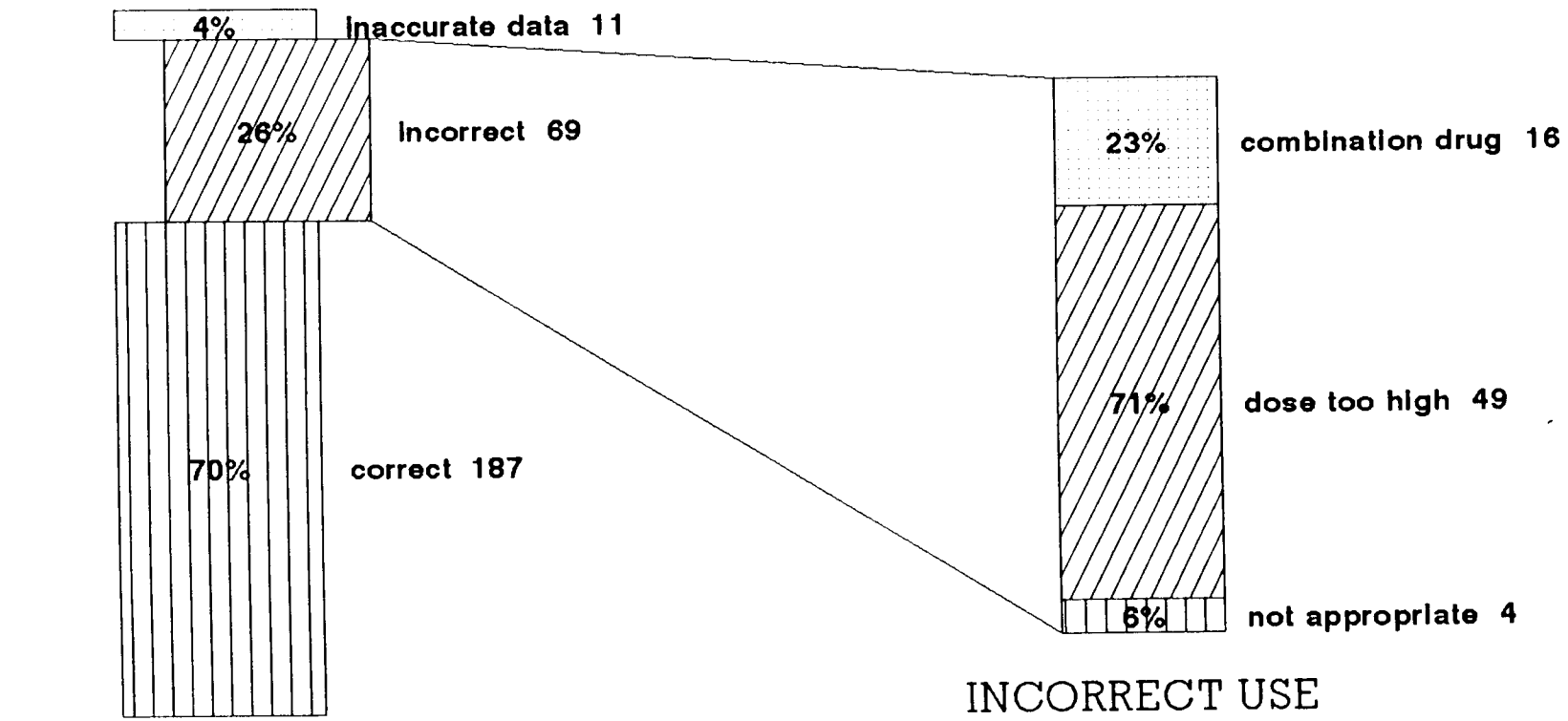


Figure 8.6.1

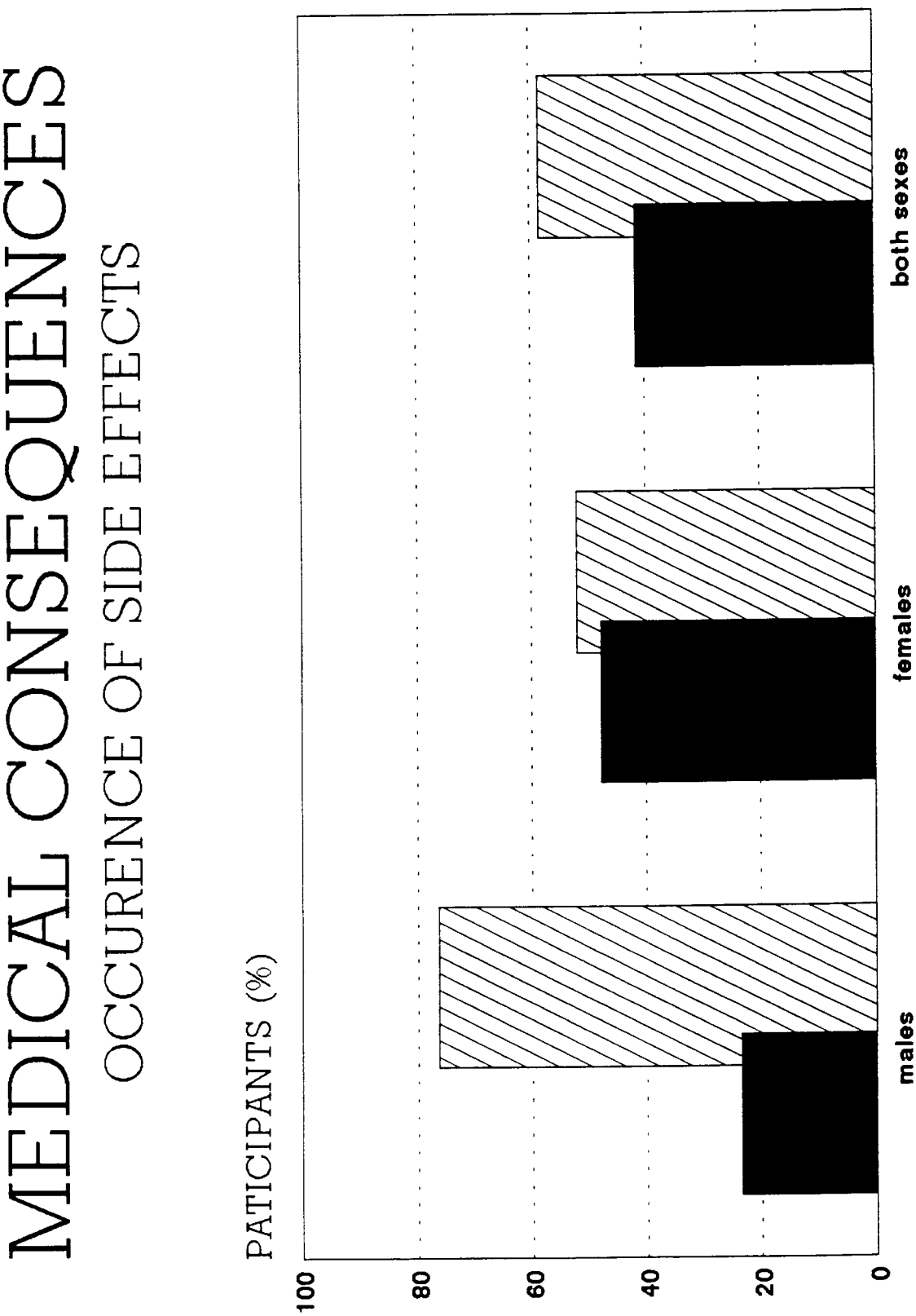
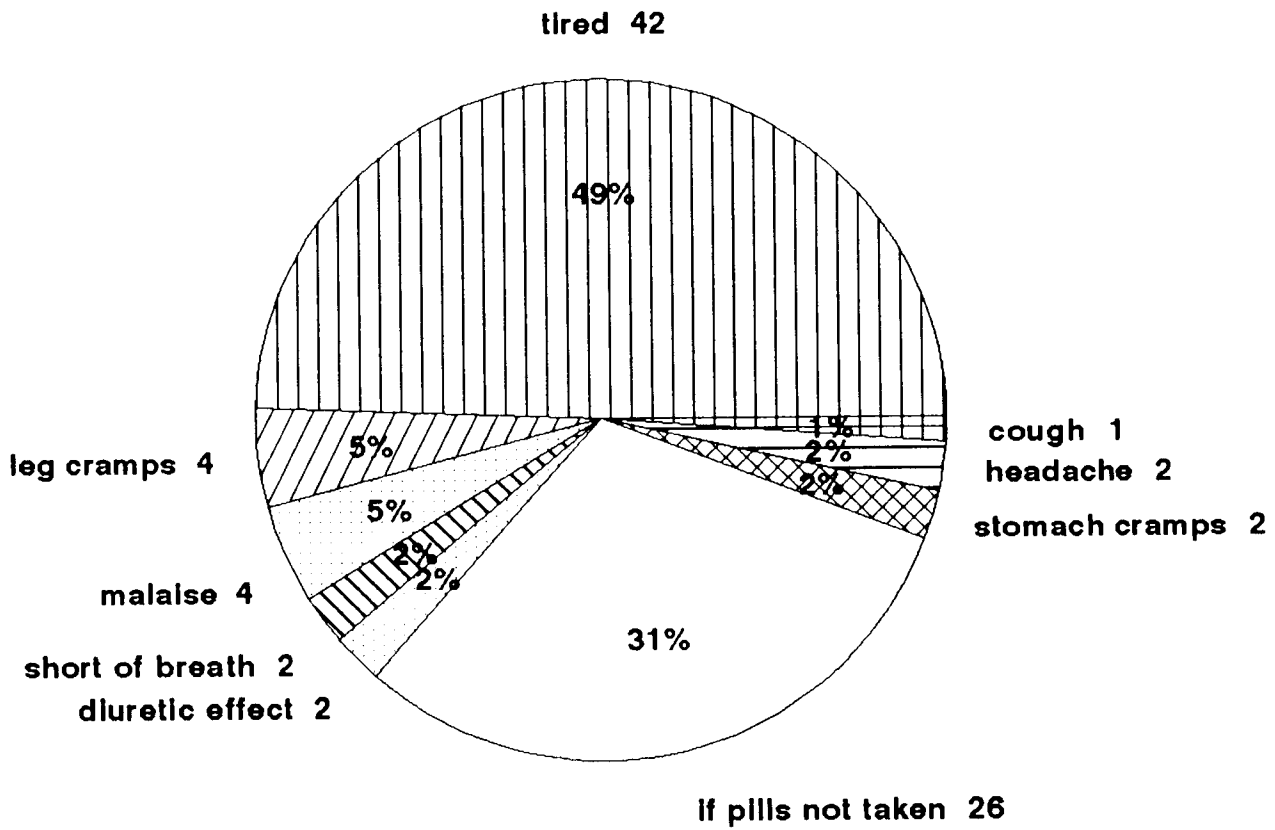

MEDICAL CONSEQUENCES
OCCURENCE OF SIDE EFFECTS
PATICIPANTS (%)
100
80
60
40
20
0
males
females
both sexes
SIDE EFFECTS EXPERIENCED
YES
NO

Figure 8.6.2.1

MEDICAL CONSEQUENCES

SIDE EFFECTS EXPERIENCED



TYPE OF SIDE EFFECT EXPERIENCED

Figure 8.6.2.2

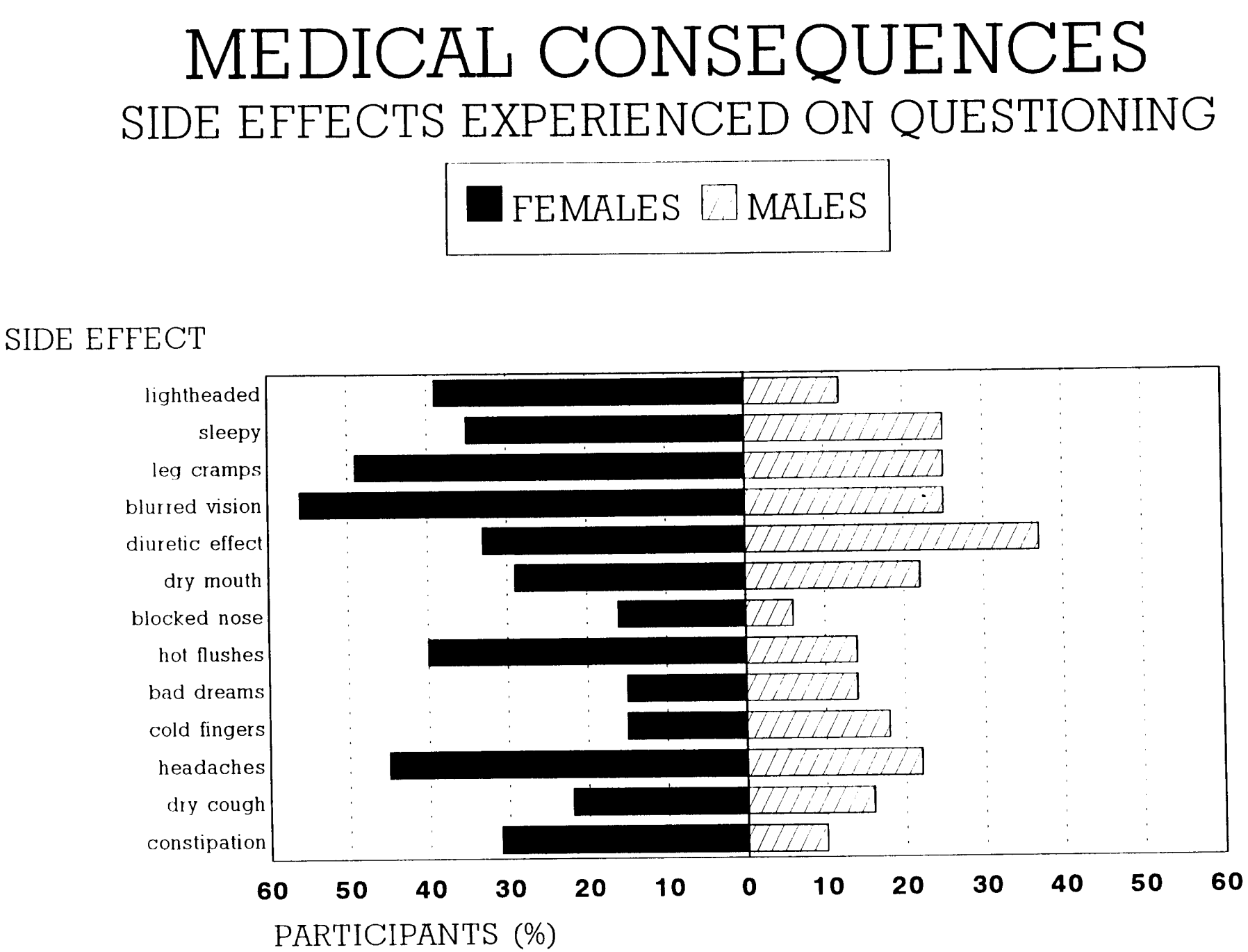

MEDICAL CONSEQUENCES
SIDE EFFECTS EXPERIENCED ON QUESTIONING
FEMALES
MALES
SIDE EFFECT
lightheaded
sleepy
leg cramps
blurred vision
diuretic effect
dry mouth
blocked nose
hot flushes
bad dreams
cold fingers
headaches
dry cough
constipation
60 50 40 30 20 10 0 10 20 30 40 50 60
PARTICIPANTS (%)

Figure 8.6.2.3

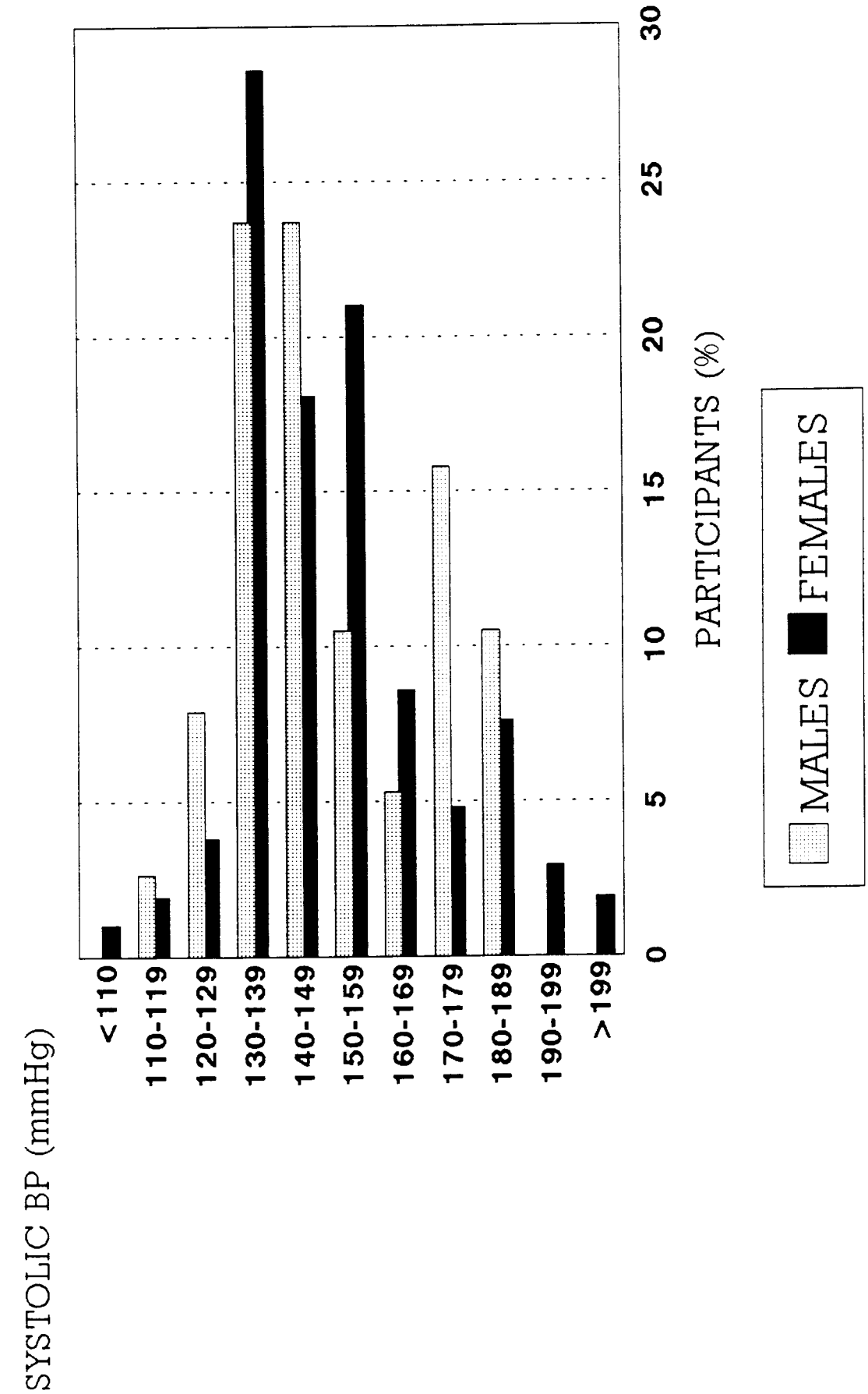

MEDICAL CONSEQUENCES
SYSTOLIC BLOOD PRESSURE
SYSTOLIC BP (mmHg)
<110
110-119
120-129
130-139
140-149
150-159
160-169
170-179
180-189
190-199
>199
0
5
10
15
20
25
30
PARTICIPANTS (%)
MALES
FEMALES

Figure 8.6.3.1

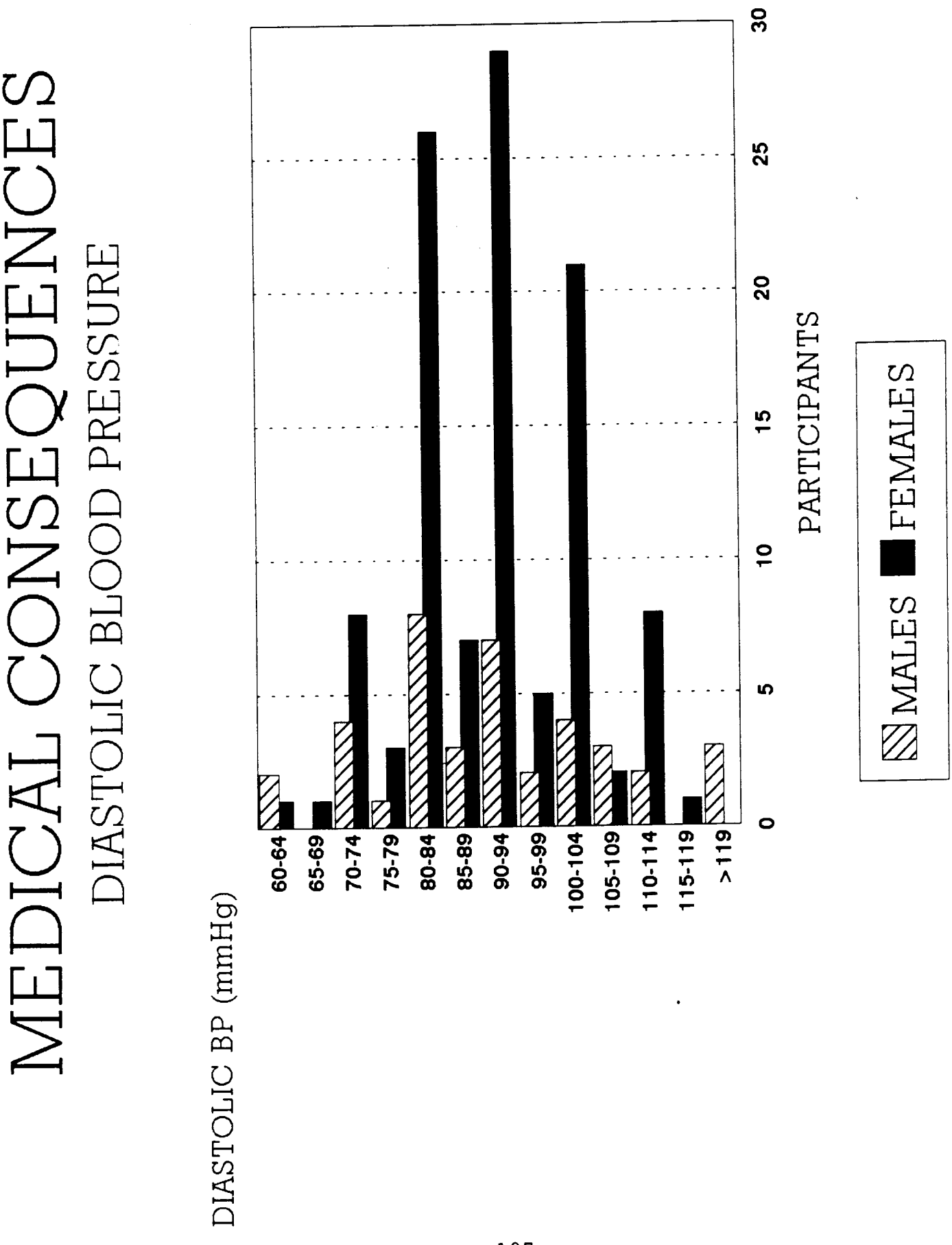

MEDICAL CONSEQUENCES
DIASTOLIC BLOOD PRESSURE
DIASTOLIC BP (mmHg)
60-64
65-69
70-74
75-79
80-84
85-89
90-94
95-99
100-104
105-109
110-114
115-119
>119
0
5
10
15
20
25
30
PARTICIPANTS
MALES
FEMALES

Figure 8.6.3.2

CHAPTER 9. DISCUSSION OF RESULTS.

1. INTRODUCTION

The purpose of this study was to develop a method to evaluate drug-use patterns in a South African community setting. Such methods have traditionally only been developed for hospital settings (Wible *et al*, 1988).

While the randomised clinical trial (RCT) study design is the best method of assessing the efficacy of a given intervention, it has certain limitations. A small, select study population is used and selection criteria can result in biases. Drug utilisation methodologies include a wider spectrum of patients - those with multiple pathological conditions, those on other medications as well as a wider age range and both sexes are described. Drug utilisation reviews describe how a drug or groups of drugs are being used in a "real" situation and what the consequences of their use are.

The major aim of this work was not to describe the study population with regard to age, sex and education level and the outcomes of the use of antihypertensive drugs, but rather to produce a picture of the management of hypertension and the medical and socioeconomic consequences of antihypertensive drug use, for this population. The data reported in this study are applicable only to the Mamre community, but the methodology is applicable to other communities or areas.

2. LIMITATIONS OF THE STUDY

The following study limitations need to be balanced against the results presented:-

(i) Interviewer bias.

The two interviewers employed had different personalities, interviewer 1 was quiet and reserved while interviewer 2 was outgoing and communicative. These personality differences resulted in different approaches to the questionnaire and different interpretations of the responses, with the result that certain data were excluded from the analysis. Attention will be drawn to the actual differences noted between the two interviewers throughout the discussion of the results.

(ii) Incomplete records.

Medical records were not available for those participants who attended the district surgeons and records for other participants were often incomplete or inconsistent. This was further complicated by the fact that 46 of the participants attended more than one medical facility. Where possible, data for participants for whom no records were available were recorded from the Mamre blood pressure monitoring station.

(iii) Observer bias.

The participants blood pressure was recorded from their medical record and was not measured by the interviewer. The variability of instruments used and the number of observers could result in a bias. Blood pressure measurements recorded from the Mamre blood

pressure monitoring station were noted to show a zero end digit preference.

(iv) Limited sample size.

Due to the limited sample size, this study could not pick up accurate incidences of side effects due to a specific antihypertensive drug, but rather showed possible trends for side effects and evaluated whether the impact of any side effects experienced by the participants influenced compliance with their antihypertensive medicines. Owing to the fact that most of the participants took only one drug, the study population was not ideal for studying drug compliance.

(v) Limited sample size.

As a result of the small sample size sub-analysis of data was often not possible and statistically significant results unless otherwise indicated have been attributed to chance.

(vi) Effectiveness of the antihypertensive drugs did not take into account the duration of treatment, the dose used, concomitant use of other drugs or the coexistence of other diseases (eg. diabetes).

(vii) Despite the translated questionnaire being reviewed by members of the community for the correct colloquial Afrikaans translation and for ease of understanding the question, the questions relating to the participants' quality of life were not clearly understood.

3. PATIENT CHARACTERISTICS

3.1 AGE AND SEX DISTRIBUTION

Patient selection may have in part accounted for the fact that nearly three quarters - 73.8% - of the study participants were females. Of the records available at the Mamre blood pressure monitoring station, for patients currently receiving treatment for hypertension, 65% are female. Furthermore, studies previously carried out in Mamre on hypertension had only focused on the female population. There does, however, appear to be a greater incidence of hypertension in the female population of Mamre. The actual sex distribution of the total Mamre population is approximately the same for both sexes (female 50.4%; male 49.6%). The male to female ratio remains about 1.0 for all ages until the age of 45, after which it drops to reflect the higher life expectancy of women (Katzenellenbogen *et al*, 1988). This picture was reflected in the study population where the mean age for the females was 59.6 as opposed to 57.8 years for the males. The oldest female participant was 85 and the oldest male 80 years.

3.2. LEVEL OF EDUCATION

The level of education attained by the study participants correlated well with the rest of the population for the same age range. A total of 32.3% of the study participants had attained at least standard 6, as opposed to 39.7% for the whole population. This lies near the figure for coloureds in the Cape Peninsula (40.9%) and is slightly higher than the national figure of 31% for coloureds (Katzenellenbogen *et al*; 1988). A difference between the two interviewers for their respondents was noted. Interviewer 1 found that 36.9% of women had a standard 6 level of education while interviewer 2 found only 25.3%. The same situation was found for the men; interviewer 1, 42.3% had a standard 6 level while interviewer 2 found 32%. Interviewer 1 recorded that 58.2% of all her respondents had a standard 6 level of education, while interviewer 2 reported only 44.2%. This difference is probably explained to a small degree by the fact that interviewer 2 had a slightly older study population (not statistically significant) than interviewer 1. Katzenellenbogen et al report that the tendency of the younger people to have a higher level of education than the older people reflects the changing educational profile of the South African population in general, and of coloured people in particular.

3.3. CHRONIC MEDICAL CONDITIONS

Apart from hypertension it was found that diabetes, rheumatic diseases and heart disease were the most frequently reported chronic illnesses. The 1988 baseline study in Mamre supports these findings (Hoffman *et al*,1988), with the one exception of a lower incidence of heart disease for men, as opposed to this study which found a higher incidence. The prevalence of tuberculosis in the community was reported to be 10,8/1 000, but none of the study participants reported that they were suffering from tuberculosis. Inquiry into a past history of tuberculosis might have corrected this discrepancy.

4. MEDICAL FACILITIES

The study participants' choice of which medical facility they would attend was largely governed by economic factors, with two-thirds of the participants attending a state facility (district surgeons, day hospital or other state hospitals). On the whole the elderly, the indigent and those on medical disability grants tended to consult the district surgeons, those on medical aids used the private doctors, while those with a small income tended to use either the day hospital in Atlantis or one of the larger hospitals in Cape Town. More respondents interviewed by interviewer 2 appeared to go to either the day hospital or to the district surgeon, but this difference was not statistically significant. Statistical differences seen here were probably due to selection bias of

respondents. Whilst none of the study participants consulted with alternative healers, the nursing staff working in Mamre reported a high use of traditional medicines by the population.

The difference between the higher number of men than women who see the same doctor at each visit, can probably be attributed to the fact that more men (33%) attend private doctors than the state facilities, as opposed to the women (25%). About sixty percent (61.5%) of participants who consult with private doctors see the same doctor at each visit.

5. DRUG USE PATTERNS

Twenty-seven different antihypertensive drugs were prescribed by the private doctors, as opposed to 20 different drugs by the doctors in state controlled facilities. The drugs used in the management of hypertension by those doctors working for state facilities are largely determined by what is available for their use on the state tender system, whereas the private doctors are not constrained in their choice of antihypertensive agents.

The drug most commonly used in this study population, methyldopa, is recommended only as a second-line agent in the management guidelines for hypertension in Southern Africa (Heart Foundation, 1992). Methyldopa is currently not considered as a first-line agent due to its side effects (sedation, lethargy, headache, blurred vision and decreased libido) and

possibly less compliance due to twice or three times daily dosing (Jackson, 1988). It is also relatively more expensive than other centrally acting agents such as reserpine (methyldopa - 9 cents/tablet; reserpine - 1 cent/tablet in the public sector).

Reserpine and other reserpine containing drugs constituted 20% of the use of antihypertensive drugs, making them the third most commonly prescribed drug for hypertension.

The management guidelines for hypertension in Southern Africa consider low-dose diuretics to be the first choice. Thiazides on their own accounted for only 7% of antihypertensives, while the combinations of amiloride or triamterene plus hydrochlorothiazide accounted for 22% of the prescribed antihypertensive drugs in the study population.

The ten most commonly taken "other" drugs correlated with the diseases of highest prevalence for the study population. Indomethacin and diclophenac were taken for rheumatic conditions; isosorbide dinitrate sublingual (5mg) and tembids (40mg) and digoxin for heart disease; metformin, glibenclamide and insulin for diabetes, and benzodiazepines for nervous conditions.

Polypharmacy, with either the antihypertensive drugs or the other drugs, was not a problem in this study population. Only 38.5% of participants took more than one antihypertensive drug and 42.6% were on antihypertensives plus a drug for other medical conditions. No

participant was on more than 4 different drugs. Participants most likely to be taking more than one drug were those who also suffered from other chronic diseases.

6. SOCIAL CONSEQUENCES

The vast majority (88.2%) of the study participants reported that they considered the medical service they attended to be either good or excellent and a similar percentage (85%) reported that they felt better since starting on antihypertensive drug treatment. This last finding is contrary to expectations, in that hypertension itself is normally asymptomatic and it is in fact the drug treatment that causes the patient to feel unwell (Mc Corvry *et al*, 1989; Williams, 1987). Since the baseline study of the Mamre community in November 1986 (Hoffman *et al*, 1988), numerous studies have been conducted in this community each year with the consequence that the Mamre population could be regarded as an over-researched community. At the time of this study another large study involving almost the entire community was being undertaken, with great personal benefit to the participants. The probability that the study participants answered these two questions in a way they thought would please the investigators, cannot be underestimated.

This study determined that approximately 60% of the participants were compliant with their antihypertensive medicines. Although the method used to estimate compliance was not one of the conventionally recognised

ones, these findings are in keeping with a previous study of female hypertensives in Mamre where a compliance rate of 72.2% was reported (Marshall *et al*, 1988). The female participants were found to be more compliant than the males (64% vs 57%). The high level of compliance in this community could in part be attributed to the establishment of the Mamre blood pressure monitoring station and its numerous educational campaigns with regard to life-style modification programmes.

An attempt was made to evaluate the impact of hypertension and the use of antihypertensive drugs on the participants' quality of life by estimating any negative impacts on performance of normal daily activities and interference with leisure or pleasure time activities. Both participants and fieldworkers were able to understand and answer the question relating to impact on their daily activities, but both groups experienced problems in interpreting the second question relating to the impact on their leisure or pleasure activities. This concept of leisure or pleasure time was not understood by this community. The consequence of the problem was that prompting by one of the fieldworkers was noted. A large number (75%) of her participants where reported to partake in some leisure activity as opposed to 23% for the other fieldworker. More specifically the first field worker noted that sixty seven respondents walked for pleasure, while only 4 respondents for the other fieldworker were found to walk as a leisure activity. This observation only became apparent after a few weeks and both interviewers were cautioned not to prompt for answers from the participants. The example of walking had been given to the fieldworkers in their training

program, so other possible examples were given to assist the fieldworkers explain this question. Unfortunately the cautionary advise was not heeded and this question had to be excluded from analysis. In retrospect the validity of such a question in a population which has an employment figure of approximately 36% requires questioning. It might have been beneficial to enlist the support of a social anthropologist during the questionnaire design phase.

7. ECONOMIC CONSEQUENCES

The figure of 24% for participants in paid employment is less than that of 64.7%, reported in 1986, for the total population (ages 15 - 65 years). This differences can be attributed to the fact that 35% of the study participants were 65 years or more as opposed to only 4.5% for the total population. The fact that such a small percentage of the study population was in paid employment detracts from the power of the data relating to time off from work due to hypertension and for the purpose of consulting a doctor for their blood pressure measurements. However, from the small sample available for analysis, hypertension does not appear to significantly adversely affect the participants' performance in the work place. Ninety one percent of those participants in paid employment were never absent from work as a consequence of their hypertension and just less than fifty percent (43.6%) took time off from work for a doctors appointment.

Despite only 24% of the study population being in paid employment, 40% of the participants were responsible for paying for their medical treatment and just under half (41%) of them reported little difficulty in paying. There was no cost to the participant if they consulted the district surgeons or if their medical aid or their employer paid. This accounted for 58% of the participants and was therefore responsible for the mode and median payment being R0.00. Participants who attended Wesfleur Day Hospital (27.2%), usually paid R5.00. The remaining 14.8% of the participants paid anything up to R95.00 for a visit to their doctor and their medicines.

The cost of antihypertensive treatment in the community was evaluated in terms of how much the payer (state, medical aid, employer or individual) paid for drugs. This cost ranged from R394.00 (in the private sector) for a month's supply of tablets to less than R1.00 (in the state sector). The large difference in the mean costs between the private and state sectors (R64.27 vs. R7.12) is largely due to the fact that drugs are infinitely cheaper when purchased through the state tender system as opposed to a private pharmacy or dispensing doctor (appendix VII). Furthermore the state tender system tends to purchase the cheapest generic brand of a drug as opposed to the more expensive original product, and little use is made of combination products which are usually more expensive than the individual agents given separately. With regards to the private sector; medical aids paid more for the same drug as opposed to the patient who bought the drug directly from the doctor. Dispensing doctors in this area had a flat rate for a consultation,

which included the cost of drugs. Those participants who were responsible paying for their own treatment, mostly consulted with private doctors, the day hospital or one the hospital in Cape Town. At all of these facilities the cost of the drug treatment was included in the overall fee and on average did not exceed R50.00. The major cost of drug treatment for hypertension in the Mamre community is therefore carried by a third party payer, namely the state or the medical aids.

8. MEDICAL CONSEQUENCES

8.1 APPROPRIATE USE OF ANTIHYPERTENSIVES

The use of antihypertensive drugs in the study population was judged to be appropriate 74% of the time, after correcting for inaccurate information from the participants. Of those judged to be incorrect, 71% were considered to be on too high a dose. The most common offenders were the thiazide diuretics and drugs containing thiazide diuretics (Moduretic^{R}, Dyazide^{R}). The currently recommended dose is 12.5mg daily, whereas doses 2 - 4 times this amount were being used (Briant, 1991). The dose of atenolol was probably also greater than what was required for hypertension. It has been shown that atenolol has a flat dose-response curve after 50mg daily (Opie, 1991). Higher doses therefore do not significantly influence hypertension control but do influence the adverse metabolic side effect profile. The use of furosemide as a single agent for the treatment of hypertension was considered to be inappropriate, except in patients with renal impairment or diabetes. The

World Health Organisation (WHO) does not recommend the use of combination drugs and therefore all combination drugs were classified as "incorrect use". Combination drugs are not advised on the grounds that the individual agents are usually cheaper than the combined drug, dosage adjustments might result in too high or too low a dose of one of the components being administered and, in the event of an adverse effect to a particular drug it is difficult to discern which is the causative agent. In this study population, however, no combination drug was used incorrectly according to the predetermined criteria.

8.2. SIDE EFFECTS OF ANTIHYPERTENSIVE TREATMENT

The questionnaire was designed to spontaneously elicit side effects that the participants perceived to be related to their antihypertensive drugs and only then prompted the participants about side effects commonly associated with antihypertensive drugs. Due to the small total sample size, incidences of side effects in this population cannot be extrapolated to expected current incidences of side effects for specific drugs. Furthermore, the experience of a certain effect could not always be separated from other potential causes.

Just over forty percent (41.5%) of the participants spontaneously reported that they experienced side effects due to their antihypertensive drugs. Double the number of women experienced side effects as opposed to the men (50% versus 23.5%). Of these participants 6.2% stopped taking the drug because of the side effects, while 9.9%

made dose adjustments. The figure of 41.5% for spontaneous reporting of side effects is low and figures as high as 70% have been reported (Dukes *et al*, 1988). Evidence that participants were responding as they thought the researcher would want, was demonstrated by the fact that 31% of these participants claimed they had unpleasant experiences if their blood pressure tablets were not taken. Short of this assumption being correct, it can only be deduced that the question was not clearly understood. The most commonly experienced side effect attributed to the antihypertensive drugs was that of tiredness (49%). This finding is in keeping with the fact that just over half (52%) the participants were on either methyldopa or reserpine-containing preparations. This side effect is well described for the centrally acting antiadrenergic drugs (appendix V).

When specifically prompted about side effects known to be associated with antihypertensive drugs, however, the most commonly occurring side effect was found to be that of blurred vision (48%), and tiredness (33%) appeared sixth in line on the list of incidences. Methyldopa and prazosin have been associated with blurred vision and thiazide diuretics with visual disturbances (Holderness *et al*, 1991; Dukes *et al*, 1988). The high incidence of blurred vision in this study population group cannot in total be attributed to the use of these agents. Although the fieldworkers were trained to exclude poor eye sight, it is possible that participants had never had their eyes tested and were unaware that they had poor eyesight. The finding that ACE inhibitors are statistically significantly associated with blurred vision, must be attributed to

chance, as these drugs have not previously been associated with this side effect. A subsequent study (Salmon J. 1993) noted an unusually high incidence of glaucoma in the female population of Mamre.

Nearly 60% of the participants were on a drug containing a thiazide or thiazide-like diuretic and these drugs could be responsible for the 43% incidence of leg cramps and that 34% of participants were troubled by frequent micturition.

The incidences of constipation (25%) and hot flushes (33%) associated with calcium antagonists and a dry cough associated with ACE inhibitors (20%) are in excess of the percentage of participants on those agents (3% and 8% respectively).

The expected incidence of dry mouth associated with methyldopa and prazosin is in the order of 0.5 - 3% (Dukes *et al*, 1988). The actual frequency reported was 53 (27%). Other commonly used drugs known to cause dry mouth are the tricyclic antidepressants and to a lesser extent the antihistamines, but neither of these two classes of drugs were used extensively in this study population.

Cold extremities or exacerbation of Raynaud's phenomenon have been associated with the use of beta-blockers. Seventeen participants (8.7%) were taking beta-blockers and 31 (16%) complained of cold fingers. The reported incidence of this effect is 0.5 - 6% (Dukes *et al*, 1988).

Bad dreams or nightmares have reportedly been associated with beta-blockers, methyldopa, prazosin and the rauwolfia alkaloid drugs. One hundred and thirty nine (71.3%) participants were taking at least one of these agents and the incidence reported was 15% which translates to 29 participants.

Methyldopa, prazosin, rauwolfia alkaloids and hydralazine have all been associated with nasal congestion, although this effect is most uncommon with hydralazine. Nasal congestion is most commonly associated with the rauwolfia alkaloids while the incidences with methyldopa and prazosin are about 0.5 - 3%. Forty eight (24.6%) participants were taking rauwolfia alkaloids, 68 (25.9%) were on methyldopa and 6 (2.3%) were on prazosin. Despite the large number of people taking agents which could cause a blocked nose the actual incidence reported (13%) is higher than would be anticipated.

The antihypertensive agents are well documented to be associated with adverse effects on sexual function. The most commonly associated agents are thiazide diuretics, beta-blockers, prazosin, spironolactone, methyldopa and hydralazine. While 86.7% of the participants used at least one of these agents, only 38 (19.5%) of them were still sexually active. Eighteen (35%) of the male participants were still sexually active and of these just over half (55.6%) were troubled by sexual dysfunction.

8.3 BLOOD PRESSURE CONTROL

When viewed in terms of the systolic blood pressure, the participants could be classified as well controlled because nearly three quarters (73%) had a systolic blood pressure of less than 160mmHg. As far as the diastolic blood pressure is concerned, less (66.3%) of the participants were controlled. When both the systolic and the diastolic blood pressure are considered together, the number of participants whose systolic blood pressure is greater than or equal to 160mmHg and/or whose diastolic blood pressure is greater than or equal to 95mmHg drops to just less than half (45.6%) of the participants. This finding is in keeping with the "rule of halves" (previously explained in Chapter 6) which states that half of those hypertensives who receive treatment will be adequately controlled.

A sub-analysis according to the medical facility where treatment was sought, revealed that those treated at the various state hospitals were the best controlled (57.4%), while those attending the private doctors were the least controlled (33.8%). The state hospitals also had the highest number of participants' blood pressures recorded. None of the 76 patients attending the District Surgeons had their blood pressures recorded, all but 16 (21.1%) of these patients had records at the Mamre blood pressure monitoring station. Nearly thirty percent (29.2%) of those participants consulting with private doctors did not have blood pressures recorded. This was more a problem of tracing the patient record as some patients continuously move between doctors or do not

consult their doctor regularly for their blood pressure. Blood pressure values not recorded within the last 6 months were excluded. Where patient files could be traced in the private sector, the blood pressure and current treatment were nearly always recorded. Twenty two percent (n=43) of the total study population did not have their blood pressure recorded.

A sub-analysis according to the drugs used to treat hypertension revealed that adequate blood pressure control was statistically significantly related to the use of methyldopa and that poor control was associated with the use of reserpine and ACE inhibitors. The poor control associated with the ACE inhibitors, could be attributed to the fact that this agent was predominantly prescribed in the private sector and the high cost of the drug could have resulted in non-compliance. On the other hand, 60% of those patients consulting a private doctor are on medical aids and therefore do not bear the cost of the drug. Most studies show ACE inhibitors to be very effective drugs with a good quality of life profile (Croog *et al*, 1986). The findings of this study could therefore be either attributed to statistical error due to the small sample size (n=21) or to the possibility that these agents are not as effective in this population. The latter possibility cannot be determined from this study as it is a purely descriptive study. A separate randomised control trial would be required to evaluate this possiblility. For the same reasons, it is also impossible to determine why methyldopa should be associated with adequate control and reserpine

with poor control when both drugs are of the same class (centrally acting agents) with a similar pharmacological spectrum of side effects.

8.4 DRUG INTERACTIONS (Detailed in Appendix VI)

Of the 107 participants who took more than one drug either for their hypertension or for another medical condition, 36.4% were at risk of a possible drug interaction.

The possible interactions were classified according to severity. None were found to be of major clinical significance, 28.2% of moderate significance and 43.6% of minor clinical significance.

Eleven (28.2%) of the interactions were classified as being due to an additive effect of individual drugs side effects because of being taken together. The most common possible side effects involved the use of the potassium-sparing/ thiazide diuretic combination products. Two of these agents were often used together resulting in cumulative adverse effects of the thiazide component. They were also used in combination with an ACE inhibitor which could possibly result in hyperkalaemia (n=8). There were seven cases of the thiazide and related diuretics being used together with the non-steroidal anti-inflammatory drugs which results in the efficacy of the thiazides being reduced.

8.5 BIOCHEMISTRY

Six of the total study population had their renal function monitored and of these 3 where known to be receiving treatment for either mild or moderate renal failure. Only one patient had his liver enzymes checked even though the most widely used drug was methyldopa. All drugs containing thiazide diuretics and the beta-blockers are known to have an adverse effects on blood potassium levels, cholesterol, glucose and uric acid levels. Six of the participants had documented potassium levels, 12 had their total cholesterol recorded and none had uric acid levels documented. The highest incidence of blood chemistry being documented was for blood glucose levels where 88 (44.8%) of the participants had a level recorded. Most of these readings were obtained from the Mamre blood pressure monitoring station where it is routine practice to do a finger-prick blood glucose level.

9. SUMMARY OF THE AVERAGE HYPERTENSIVE PATIENT IN THE STUDY POPULATION

The average hypertensive patient in the study population was a 59 - 60 year old female, with a standard 5 or 6 education.
She would have about a 33% probability of also suffering from joint pains, diabetes or heart problems and would be taking one drug for the relevant condition.

She would consult with either one of the district surgeons or with a doctor at Wesfleur Hospital in Atlantis and would be unlikely to see the same doctor at each follow-up visit. The doctor would prescribe one of the following drugs for her hypertension; methyldopa, amiloride co. or a reserpine/rauwolfia containing drug.

The patient will be very satisfied with the medical care she is receiving, perceive herself to feel much better when she takes her tablets correctly and will probably be compliant.

She will most probably be in unpaid employment or a pensioner. The average cost of her medicines to the state for a one months supply will be R7.12. She will pay on average R3.00 per visit to the doctor and most often will find herself financially burdened.

She will have a 50% chance of experiencing side effects due to her antihypertensive drug, but is unlikely to stop taking her medicine. The

most likely side effects experienced will be blurred vision, leg cramps, headaches and urinary frequency due to the diuretic effect. She is unlikely to be at risk of experiencing a drug interaction, but if she is taking any other medicines the incidence of experiencing a drug interaction is 33-50%. The probability that her blood pressure is controlled is just less than 50%.

CHAPTER 10. CONCLUSION AND RECOMMENDATIONS

CONCLUSION

What can be concluded from this research has largely been covered in the discussion of the results and the conclusions reached are only applicable to the Mamre community.

1. The participants' perception of their well being was not impaired by their use of antihypertensive drugs and the side effects of these agents did not appear to interfere with the normal everyday activities of the participants.

2. The major burden for the cost of antihypertensive drug treatment was borne by the state and the medical aid companies and not by the study participants. However, of the 78 (40%) participants who had to pay for their own treatment, just over fifty percent could not afford it.

3. More than twenty different doctors prescribed 27 different antihypertensive drugs to the 195 study participants. The overall use of these agents was largely considered to be appropriate and blood pressure was controlled in about 50% of the participants, for whom medical records were available. The assumption was made that the initial diagnosis of hypertension was correct.

4. While the cost of the drugs prescribed ranged from 1.1 cents to 410.6 cents for an average daily dose depending on which medical facility the participant attended, blood pressure control did not improve with increasing drug cost. In fact, control decreased with increasing drug costs.

RECOMMENDATIONS

Arising from the findings of this study and the insight gained, the following recommendations are made:

1. The assistance of a social anthropologist is essential in developing "quality of life" assessment tools for antihypertensive drugs, which will be applicable to the various South African ethnic groups.

2. Similar research projects need to be undertaken in other parts of the country and amongst other population groups. The drug use patterns of antihypertensive drugs and the consequences of their use should be established and correlated for the whole South African population before a definitive guideline for the management and treatment of hypertension is compiled.

3. Arising from the finding that ACE inhibitors were found to be associated with poor blood pressure control, further studies would

be helpful in determining the efficacy of ACE inhibitors in this sub-set of the population.

4. Although the use of antihypertensive agents on the whole were found to be appropriate, the dose was evaluated as being too high in 49 instances. The doses used, however, did not exceed those recommended in the package inserts. Continuing education of all health professionals in the management of hypertension and in the new developments is therefore essential in order to prevent unnecessary or excessive drug treatment, which often does not improve the medical outcome and only contributes to greater side effects. Emphasis should also be placed on the importance of keeping accurate patient records.

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APPENDIX I

GLOSSARY OF TERMS

1. BACKGROUND DATA

Patient background data refers to the patients age, sex, education level, diseases that they might suffer from and how these diseases are being treated. Background data on the prescriber refers to the year of qualification, the university attended and any additional qualifications of the doctor.

2. BASELINE DATA

Baseline data refers to what drugs are being used in the treatment of hypertension, how the drugs are being used and who is prescribing the drugs.

3. COST-BENEFIT ANALYSIS

Cost-benefit analysis is more strictly confined to studies where both the resources used in an activity and the benefits which it can yield can be expressed in monetary terms and therefore forces an explicit decision on whether the cost is worth the benefit (Eisenberg John M, 1989).

4. COST-EFFECTIVENESS ANALYSIS

Cost-effectiveness analysis measures the net cost of providing a service as well as the outcomes obtained. No clinical service or treatment can be considered cost effective in isolation, it must be compared with at least one other service or treatment. Therefore cost effectiveness analysis compare the cost of achieving the same outcome by a variety of different methods
(Eisenberg John M, 1989).

5. DRUG INTERACTIONS

An interaction is said to occur when the effects of one drug are changed by the presence of another drug, food, drink or by some environmental chemical agent. For the purpose of this study interactions have been classified into 4 sub-groups:-

(a) Major Clinical Significance -
An interaction which has the potential to harm the patient.

(b) Moderate Clinical Significance -
An interaction where the potential to harm the patient is less.

(c) Minor Clinical Significance -
An interaction where the potential to harm the patient is slight or the incidence of the interaction is quite low.

(d) Exacerbation of Side Effects -
The concomitant use of drugs results in the side effects of one or both of the drugs being "additive" (Hansten PD. 1985).

6. DRUG UTILISATION REVIEW

The World Health Organisation defines drug utilisation review as the marketing, distribution, prescription and the use of drugs in a society, with special emphasis on the resulting medical, social and economic consequences (Grimsson, 1980).

7. EXPLICIT CRITERIA

Explicit criteria are predetermined elements (by consensus) of health care against which aspects of the quality, medical necessity and the appropriateness of a health service may be compared. Explicit criteria are usually written and very specific as opposed to implicit criteria which are normally unstructured, un written and hence individually determined (Gregoire, 1987).

8. PRIMARY HEALTH CARE

Primary health care as defined by the World Health Organisation is essential health care based on practical, scientifically sound and socially acceptable methods and technology made universally accessible to individuals and families in the community through their full participation and at a cost that the community and the country can afford to maintain at every stage of their development in the spirit of self-reliance and self-determination.----------.It is the first level of the contact of individuals, the family and the community with the national health system bringing health care as close

as possible to where people live and work, and constitutes the first element of a continuing health care process (Mathews *et al*, 1989).

10. QUALITY OF LIFE

Quality of life is normally assessed in terms of the ability of an individual to contribute fully to, and derive satisfaction from, the normal activities of life, including work, marriage, family life and leisure activities. It may also be assessed in terms of freedom from physical and psychiatric symptoms and from the impairment in physical and mental functioning (Seedat, 1991).

11. ATC *(Anatomical, Therapeutic* and *Chemical)* CLASSIFICATION INDEX

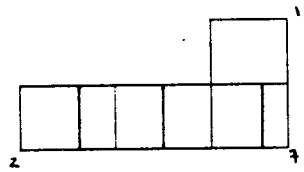
This is a classification index devised by the Nordic council on Medicines and the WHO Collaborating Centre for Drug Statistics Methodology. It groups pharmaceutical agents according to their therapeutic indication and is now widely used in drug utilisation studies.

APPENDIX II

DRUG UTILISATION REVIEW : PATIENT QUESTIONNAIRE

Name of field worker: _____

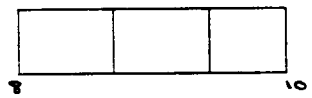
Date of interview: ___/___/__



SECTION A : BACKGROUND DATA

(1) Patient name:
_____

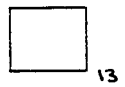
(2) Project number:



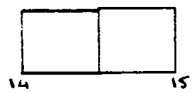
(3) Place of residence:
_____

(4) Date of birth:
___/___/___

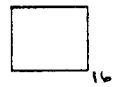
(5) Sex:
(1) female
(2) male



(6) What level of schooling or post level schooling do you have?
_____



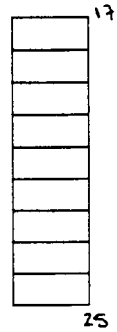
(7) (a) Do you suffer from any diseases?
(1) yes
(2) no



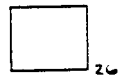
If you answered yes, what do you suffer from?
_____

(b) Do you suffer from any of the following diseases?

(1) asthma
(2) diabetes
(3) renal disease
(4) heart disease
(5) TB
(6) high cholesterol
(7) hypertension
(8) "gout"
(9) other



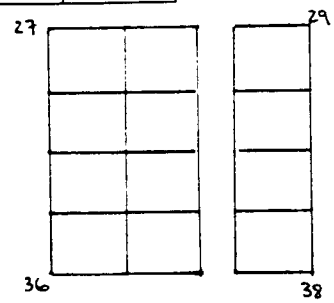
(8) Are you taking any pills for any of these diseases?
(1) yes
(2) no



If no, ignore question 9 and proceed to section B.

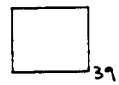
(9) If yes, what medicines are you taking? (medicines for hypertension must be recorded in section B, question 2.

Drug	Dose	Route	Freq	Duration	Dx



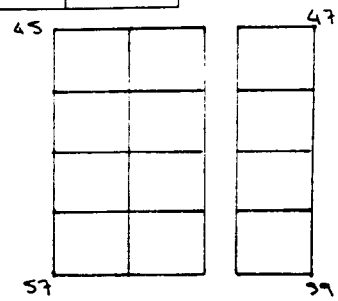
SECTION B : PROCESS DATA

(1) Do you know if you have high blood pressure?
(1) yes
(2) no



(2) What medicines are you taking for your blood pressure? (Tick in the column SEEN if you confirmed the data with by seeing the tablets and packets)

Drug	Dose	Route	Freq	Duration	Seen



(3) Where do you go for treatment for your blood pressure?

(1) Day hospital (name_____)
(2) District surgeon (place_____)
(3) GP (place_____)
(4) PHC clinic (place_____)
(5) Hospital clinic / out patients (name_____)
(6) Other (specify_____)

60 65

(4) When you see a doctor, do you always see the same doctor?

(1) yes
(2) no

Comment:_____
_____

Doctors name:_____

66 67

SECTION C : OUTCOME DATA

1 3

I. SOCIAL CONSEQUENCES

(1) How do you rate the medical service that you receive?

(1) excellent
(2) good
(3) average
(4) poor
(5) completely useless

4

Why?_____
_____

(2) In general how do you feel since starting treatment?

(1) better
(2) the same
(3) worse

5

Comments:_____
_____

(3) During the last month have you been unable, due to your health, to carry out your usual activities around the house and garden?

(1) normal activities performed
(2) activities carried out alone with effort
(3) activities carried out with assistance
(4) completely disabled

If the reply was number 1, proceed to question 5.

(4) What were the reasons that you were unable to carry out your normal activities?

_____
_____

(5) Do you have any leisure and / or pleasure activities?

(1) yes
(2) no

If no, ignore questions 6 and 7 and proceed to the next section.

(6) If yes, please list these activities.

_____
_____
_____

(7) Has your state of health interfered with these activities recently?

(1) normal activities possible
(2) carried out alone but with effort
(3) only achieved with assistance
(4) unable to carry out any of these activities

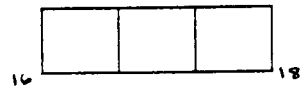
II. ECONOMIC CONSEQUENCES

(1) Tick the answer that best explains your situation?

(1) In paid employment (fulltime / part time)
(2) not in paid employment but working around the house or looking after relatives etc.
(3) unemployed but looking for work
(4) unemployed for medical reasons (specify___ _____)
(5) pensioner

(2) Who pays for your medicines?
(1) no cost (eg. State pays)
(2) self
(3) employer
(4) medical aid / benefit
(5) other (specify_____)

(3) If you pay in full each month for your medicines, how much do you pay?
R_____



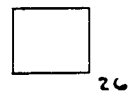
(4) How much do you pay to see the doctor?
R_____

Can you afford to pay for your medicines and to see the doctor?_____
_____

(5) How many days did you take off work last month due to your high blood pressure?_____days

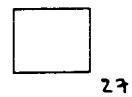
(6) Do you have to take time off work to see the doctor or to collect medicines?
(1) yes (specify the hours taken off an average each week _____hours)
(2) no

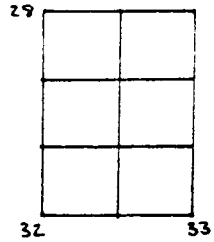
(7) Do you still receive your pay if you take off time to see your doctor?
(1) yes (100% received)
(2) >50% received
(3) <50% received
(4) no (0% received)



III. MEDICAL CONSEQUENCES

(1)(a) Have you ever experienced any side effects or unpleasant experiences since starting your blood pressure tablets?
(1) yes (specify_____
_____)
(2) no





(1)(b) Do any of the unpleasant effects of your medicine prevent you from taking your tablets as prescribed?

(1) yes
(2) nearly always
(3) hardly ever
(4) no

34

Comments: _____

_____

QUESTIONS 2 TO 16: IF THE RESPONDENTS ANSWERS YES, THEN PLEASE WRITE "STOPPED" NEXT TO THE ANSWER IF THE EFFECTS CAUSED THE TABLETS NOT TO BE TAKEN.

(2) In the last month have you suffered from light-headedness, faintness or dizziness?

(1) yes (specify when it happens _____)

(2) no

35 36

(3) In the last month have you often felt unusually sleepy during the day?

(1) yes
(2) no

37

(4) Have you in the last month noticed weakness in the limbs?

(1) yes
(2) no

38

(5) Have you in the last month had blurring of vision?

(1) yes
(2) no

39

(6) How many times, on average, do you rise at night to pass urine?

(1) 0
(2) 1
(3) 2
(4) more than twice (specify)

40 41

(7)(a) In the last month have you suffered from a dry mouth?
(1) yes
(2) no

42

If no, proceed to question 8

(7)(b) If yes, does the dry mouth interfere with talking or eating?
(1) yes
(2) no

43

(8) In the last month have you ever been troubled by a blocked nose (other than when you have had a cold)?
(1) yes
(2) no

44

(9) In the last month have you ever felt flushing of the face or neck?
(1) yes
(2) no

45

(10) Within the last month has there been a change in what you dream about?
(1) yes
(2) no

46

(11)(a) Do your fingers go white in the cold weather?
(1) yes
(2) no

47

If no, proceed to question 12

(11)(b) If yes, do they become painful?
(1) yes
(2) no

48

(12)(a) Have you, in the last month, suffered from headaches?
(1) yes
(2) no

49

If no, proceed to question 13

(12)(b) If yes, how often do the headaches occur?
(1) less than 1 per week
(2) 1-6 times a week
(3) 1 or more times per day

50

(13) In the last month have you suffered from a dry cough?
(1) yes
(2) no
S1

(14) Have you in the last month been unusually constipated?
(1) yes
(2) no
S2

Questions 16 and 17 relate to your sex life. While we appreciate that this information is of a personal nature, we are interested in all aspects of your well being and would like you to answer them.

(16)(a) Do you have sexual intercourse?
(1) yes
(2) no (specify if this is for any medical reason_____)
S3

(16)(b) Is your interest in sex-
(1) less
(2) the same
(3) greater
than before you started taking your blood pressure tablets?
S4

(17)(a) FOR MEN ONLY
During sexual intercourse are you troubled by failure to sustain an erection?
(1) yes
(2) no
S5

(17)(b) During intercourse are you troubled by failure to ejaculate?
(1) yes
(2) no
S6

---

(1) Identified from baseline survey
(2) Identified from Mamre BP clinic
(3) Both 1 and 2
(4) Identified by health workers in the area
S7

Mamre blood pressure number:
_____

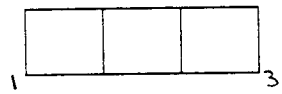
APPENDIX III

DRUG UTILISATION REVIEW : DOCTORS' RECORDS

(1) Patient name:

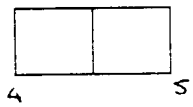
_____

(2) Project number:



(3) Name of doctor:

_____

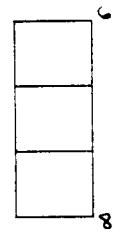


(4) Chronic diseases recorded by the doctor:

(1) _____

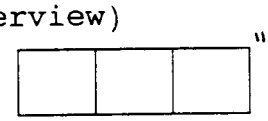
(2) _____

(3) _____

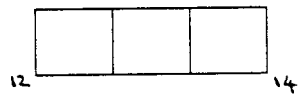


(5) Blood pressure (nearest to date of interview)

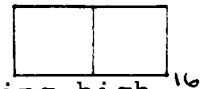
(1) systolic _____mmHg



(2) diastolic _____mmHg



Date of the blood pressure reading ____/____/19___

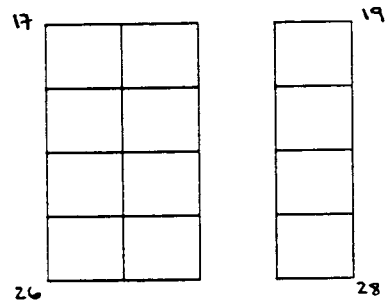


(6) When was the patient first diagnosed as having high pressure?

____/19___

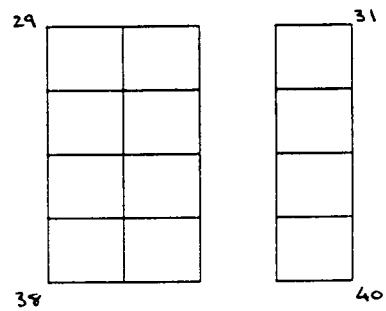
(7) What medicines have been prescribed for the high blood pressure?

Drug	Dose	Route	Freq.	Durat.
1.				
2.				
3.				
4.				



(8) What other medicines have been prescribed?

Drug	Dose	Route	Freq.	Indic.
1.				
2.				
3.				
4.				



BIOCHEMISTRY RESULTS

(9) Renal function:

_____ (1) normal
(2) mild renal failure
(3) moderate renal failure
(4) severe renal failure
(5) not recorded

☐ 41

(10) Liver function:

_____ (1) normal
(2) raised liver enzymes
(3) not recorded

☐ 42

(11) Potassium level:

_____ (1) normal range
(2) high
(3) low
(4) not recorded

☐ 43

(12) Cholesterol level:

	(a) HDL	(b) LDL	(c) Total Cholesterol	
(1) normal range:	_____	_____	_____	☐ 44
(2) high :	_____	_____	_____	☐ 45
(3) low :	_____	_____	_____	☐ 46
(4) not recorded:	_____	_____	_____	

(13) Blood glucose:

_____ (1) normal
(2) raised
(3) not recorded

☐ 47

(14) Uric acid:

_____ (1) normal
(2) raised
(3) not recorded

☐ 48

APPENDIX IV

DRUG UTILISATION REVIEW : PRESCRIBER DATA

(1) Doctors name:
_____

☐☐ 2

(2) Place of work:

(1) private practice
(2) district surgeon
(3) day hospital
(4) teaching hospital

☐ 3

(3) University attended :_____

Town :_____

Country :_____

☐
☐
☐ 6

(4) Year of graduation:

19____ (years in practice:_____)

☐☐ 8

(5) Additional qualifications:
_____
_____
_____

☐
☐ 10

APPENDIX V.

ANTIHYPERTENSIVE DRUG PROFILES.

These profiles are not intended to be complete reference works. Unless otherwise indicated the greater part of these profiles have been compiled from the following reference sources :-

Therapeutic Drugs (Dollery *et al*, 1991)

The South African Medicines Formulary (Holderness *et al*, 1991)

The American Hospital Formulary Service (McEvoy *et al*, 1993)

Martindale, The Extra Pharmacopeia (Reynolds *et al*, 1989)

Drugs for the heart (Opie, 1991).

These protocols, together with the manufacturer's package insert of the drug, were used as the criteria for assessing the appropriate use of antihypertensive drugs in the study population.

ANTIADRENERGICS, CENTRALLY ACTING

RESERPINE

MECHANISM OF ACTION :

Reserpine acts by binding to and destroying the granular noradrenaline storage vesicles in central and peripheral adrenergic neurons, resulting in the nerve endings losing their ability to concentrate and store noradrenaline and dopamine (Goodman & Gilman, 1990). Catecholamines leak into the cytoplasm, where they are destroyed by intraneuronal monoamine oxidase, and little or no active transmitter is discharged from nerve endings when they are depolarised.

The depletion of noradrenaline rather than the CNS effect is thought to be responsible for the antihypertensive effect. Reserpine reduces both cardiac output and peripheral resistance.

PHARMACOKINETICS :

The elimination $T_{1/2}$ is in the order of 1 - 2 weeks and effects may persist for many days or weeks after the drug is stopped.

ADVERSE EFFECTS :

The adverse effects are usually dose related. The most common adverse effect are drowsiness, fatigue, dizziness, depression, decreased libido and nasal stuffiness

DOSE :

Reserpine's kinetics allow once daily dosage (0.05 - 0.1 mg) (Opie, 1991) and ensure that sporadic missed doses have little or no effect on blood pressure levels (Luxenberg & Feigenbaum, 1983).

METHYLDOPA

MECHANISM OF ACTION :

Methyldopa is metabolised to false transmitters in the brain and this central effect is thought to be responsible for its antihypertensive activity (Goodman & Gilman, 1990). It reduces sympathetic outflow from the CNS and a decrease in plasma renin activity. The long-term hypotensive effect is accompanied by a decrease in both cardiac output and peripheral resistance (Jackson, 1988).

PHARMACOKINETICS :

The plasma $T_{1/2}$ is 1 - 2 hours, with hypotensive activity lasting between 10 - 24 hours. The onset of action is slow and oral bioavailability is low because of poor absorption and extensive first-pass metabolism.

ADVERSE EFFECTS :

It commonly causes sedation, lethargy, forgetfulness and the inability to concentrate (Jackson, 1988). Other frequently occurring side effects are headache, dizziness, blurred vision, decreased libido and dry mouth.

DOSE :

A dose of up to 2 - 3g per day in two to three divided doses may be required for hypertension.

ANTIADRENERGICS, PERIPHERALLY ACTING

PRAZOSIN /DOXAZOSIN

MECHANISM OF ACTION :

They block the post-synaptic alpha$_1$-adrenergic receptors causing dilatation of both the peripheral arterial and venous systems. This leads to a fall in peripheral vascular resistance and in venous return to the heart (Goodman & Gilman, 1990).

PHARMACOKINETICS :

~~Brazes~~ Prazosin undergoes substantial first-pass metabolism and oral bioavailability varies widely (40 - 80%) (Goodman & Gilman, 1990). Onset of antihypertensive effect is within 2 hours, but weeks may be required for optimal efficacy. The plasma $T_{1/2}$ is 3 hours, and the duration of action of brazes is 4 - 6 hours. Brazes is metabolised in the liver are excreted in the bile and faeces.

ADVERSE EFFECTS :

Most commonly they cause dizziness, lack of energy, palpitations, weakness, drowsiness, headache, first dose orthostatic hypotension and nausea. These effects may be diminished with continuous therapy or may be relieved by a reduction in dosage.

DOSE :

The recommended starting dose is 0.5mg twice or three 3 times a day, increasing slowly to a daily dose not greater than 20mg.

AGENTS ACTING ON ARTERIOLAR SMOOTH MUSCLE

HYDRAZINOPHTHALAZINE DERIVATIVES

HYDRALAZINE

MECHANISM OF ACTION :

It acts directly on arterial smooth muscle to cause vasodilation and a reduction in total peripheral vascular resistance. Hydralazine decreases the diastolic more than the systolic blood pressure by lowering peripheral resistance (McAreavey *et al*, 1984). It increases heart rate, stroke volume and cardiac output.

PHARMACOKINETICS :

The oral biovailability of hydralazine is low (30 -50%) due to first-pass metabolism and may vary according to acetylator status (Goodman & Gilman, 1990). The plasma $T_{1/2}$ is about 1 hour, but antihypertensive effects persists for considerably longer (12 hours) because the drug is taken up by the arterial wall. Hydralazine is acetylated in the liver then excreted via the kidney.

ADVERSE EFFECTS :

The most frequently occurring adverse effects are headache, palpitations, postural hypotension and tachycardia. After 2 months use or with doses exceeding 200mg daily or in slow acetylators a syndrome resembling systemic lupus erythematosus and rheumatoid like arthropathy may occur.

DOSE :

The usual starting dose is 20 - 25 mg twice daily, increasing gradually to 25 - 75 mg every 6 - 8 hours.

CALCIUM ANTAGONISTS

MECHANISM OF ACTION :

As a class their dominant effect is a decrease in peripheral vascular resistance. They limit calcium ion entry via the voltage-sensitive (slow) calcium channel, thereby reducing availability of calcium from the sarcoplasmic reticulum and decreasing contractility of arterial muscle. The different drugs have varying effects on cardiac rate, conduction and contractile force.

VERAPAMIL

PHARMACOKINETICS :

Oral bioavailability is small (20 - 30%) due to first-pass metabolism in the liver. The elimination $T_{1/2}$ is 3 - 7 hours, but can be up to 12 hours with repeated doses. Several metabolites are formed in the liver, and approximately 70% of the drug and its metabolites are excreted in the liver. Norverapamil is an active metabolite and may accumulate in renal impairment.

ADVERSE EFFECTS :

Verapamil frequently causes the transient elevation of liver enzymes. Other effects include constipation, nausea, headache, dizziness, fatigue and facial

flushing. Females may be troubled by ankle swelling not due to fluid retention.

DOSE :

Oral doses of verapamil are usually 80 - 120mg three times a day. For maintenance treatment with the slow-release preparations a twice daily dose of 240 - 360 mg should be adequate.

NIFEDIPINE

MECHANISM OF ACTION :

Nifedipine has the greatest vasodilator effect of the calcium antagonists, but has minimal effect on conduction. It is a dihydropyridine calcium antagonist and inhibits the calcium channel by acting at a binding site different to that of verapamil.

PHARMACOKINETICS :

It is almost completely absorbed, but oral bioavailability is reduced to 60 - 75% by first-pass hepatic metabolism. The plasma $T_{1/2}$ is 2 - 6 hours. Hypotensive effects occur within 15 - 30 minutes after an oral dose and within 2 - 3 minutes if the capsule is broken and the liquid contents swallowed. Nifedipine is completely metabolised in the liver, with 85% of the inactive metabolites being excreted in the urine.

DOSE :

In mild to moderate hypertension, the required dose as monotherapy is about 10 - 20 mg three times a day. A starting dose of 5 mg should be used in the elderly to avoid possible cerebral underperfusion.

DILTIAZEM

MECHANISM OF ACTION :

Diltiazem is a peripheral vasodilator, with mild negative inotropic effects (Buckley M *et al*, 1991). Its mechanism of action is similar to that of verapamil, but the reduction in blood pressure is usually accomplished without reflex tachycardia, probably due to its suppression of sinoatrial node stimulation.

PHARMACOKINETICS :

It is well absorbed, but due to first pass metabolism in the liver only 45% is bioavailable. The onset of action is within 15 - 30 minutes, but the maximum hypertensive effect occurs at 1 - 2 hours. The plasma $T_{1/2}$ is 2 - 11 hours, but averages 4.5 hours. Diltiazem is acetylated in the liver and eliminated by the kidneys (35%) and the GI tract (65%).

DOSE :

The usual initial dose is 60mg three to four times a day, increasing if necessary at one to two day intervals to 90 mg three or four times a day, to a maximum daily dose of 360mg.

NON-THIAZIDE SULFONAMIDES

INDAPAMIDE

MECHANISM OF ACTION :

Its chemical structure similar to the thiazides and is best regarded as a thiazide-like diuretic. The primary antihypertensive action is thought to be due to inhibition of net inward flow of calcium, thereby inhibiting the resultant phasic contractions in vascular smooth muscle.

PHARMACOKINETICS :

Oral absorption is rapid and high and its duration of action is 16 - 36 hours and the terminal half life is 14 - 16 hours. Indapamide is extensively metabolised in the liver and its major route of excretion is the kidneys.

ADVERSE EFFECTS :

There is a low incidence of CNS side effects, e.g. headache, dizziness and lassitude. With long term use mild hypokalaemia may occur.

DOSE :

A single dose of 2.5mg in the morning is sufficient in 70 - 80% of patients with mild hypertension.

AGENTS ACTING ON RENIN-ANGIOTENSIN SYSTEM

MECHANISM OF ACTION :

ACE inhibitors appear to lower the blood pressure by a number of mechanisms. Firstly, angiotensin converting enzyme is responsible for converting angiotensin I to angiotensin II (a potent vasoconstrictor and stimulator of aldosterone secretion) and for the breakdown of bradykinin (a vasodilator). Secondly, specific vasodilation may enhance natriuresis and thirdly by preventing reabsorption of sodium by aldosterone to reduce natriuresis. Fourthly, they reduce the inactivation of vasodilatory bradykinins. The other mechanisms are the inhibition of local formation of angiotensin II in the vascular tissue and in the myocardium and by modulating the sympathetic nervous system pre- and post synaptically. This antisympathetic action of ACE inhibition also contributes to their antihypertensive effect.

CAPTOPRIL

PHARMACOKINETICS :

About 60 - 75% is absorbed and the elimination $T_{1/2}$ is 2 - 3 hours but the duration of action is approximately 6 - 8 hours. Its antihypertensive effects may last for up to 12 hours. It is partly metabolised in the liver and 40 - 50% of the oral dose is excreted unchanged in the urine.

ADVERSE EFFECTS :

The most commonly occurring adverse effects are first dose hypotension, disturbances in taste, a dry hacking cough and skin rashes. Proteinuria and angioedema occur less frequently.

DOSE :

Treatment is usually started with a dose of 6.25mg, which is then increased over several weeks to a maximum dose of 150 mg daily, given in 2 divided doses.

ENALAPRIL

Enalapril is de-esterified in the liver and the kidney to the active compound, enalaprilat (Opie, 1991). It is a more potent ACE inhibitor than captopril.

PHARMACOKINETICS :

About 55 - 75% of the oral dose is rapidly absorbed. The time to peak serum concentration is about 2 hours for enalapril and 5 hours for enalaprilat. 95% of either enalapril or enalaprilat is excreted via the kidneys. In hypertension the elimination $T_{1/2}$ for enalaprilat is 4 - 5 hours, but increases to about 11 hours after multiple doses.

ADVERSE EFFECTS :

Without the SH group of captopril the immune-based toxic effects (neutropenia and proteinuria) are very rare. The other side effects of captopril are common to enalapril. Dizziness and headache are frequently and fatigue has also ben reported with enalapril.

DOSE :

Patients are usually started on a dose of 2.5 - 5 mg daily and this may then be increased to a dose of 10 - 20 mg as a single daily dose, however a twice daily dosage may also be given.

LISINOPRIL

Lisinopril is a lysine derivative of enalaprilat and does not require hydrolysis to become active. Lisinopril also has a higher affinity for ACE than captopril.

PHARMACOKINETICS :

Lisinopril is slowly absorbed after an oral dose and its hypotensive effects start 2 hours after ingestion with peak at 4 to 8 hours. It is not metabolised and 30% is excreted unchanged by the kidneys and 60% in the faeces. The plasma $T_{1/2}$ is 12 - 14 hours, with a duration of action exceeding 24 hours.

DOSE :

The initial dose 2.5 to 5 mg with a maintenance dose of 20 mg as a single daily dose.

RAMIPRIL

Ramipril binds rapidly to form an initial enzyme-inhibitor complex which then slowly undergoes isomerisation to give complete inhibition. The subsequent low dissociation rate contributes to the high potency and long duration of action of the drug.

PHARMACOKINETICS :

Ramapril is rapidly hydrolysed in the liver to ramiprilat; some hydrolysis may occur across the intestinal wall. The kidneys are the main route of

elimination. The plasma $T_{1/2}$ of ramiprilat is 1 - 4.5 hours with a mean of 3 hours.

DOSE :

A starting dose of 2.5 mg daily is used and this is increased gradually over 1 - 2 weeks to a dose of 5 - 10 mg daily.

DIURETICS

LOW-CEILING DIURETICS, THIAZIDES

THIAZIDE DIURETICS

MECHANISM OF ACTION :

Thiazide diuretics are sulphonamide derivatives. Initially blood pressure is lowered by a combination of inhibition of sodium and chloride reabsorption in the early distal tubule and a direct effect of the drug on the vascular smooth muscle (Tarazi *et al*, 1970). The long term hypotensive effect is associated with a reduction in total peripheral resistance (Jackson, 1988). Excretion of potassium, magnesium and zinc is enhanced while calcium excretion is diminished. Low doses are used in the long term management of hypertension, high doses cause side effects (Briant RH, 1991). The dose response curve with respect to blood pressure is very flat, therefore increasing the dose beyond a certain minimum only causes trouble.

HYDROCHLORTHIAZIDE (HCTZ)

PHARMACOKINETICS :

The oral bioavailability is about 70% and the onset of diuretic action is within 2 hours and lasts for 6 - 12 hours, but the hypotensive effect may take 3 - 4 days before becoming evident. Maximum blood pressure reduction occurs after about 8 weeks of therapy (Leary, 1989). Hydrochlorothiazides biological $T_{1/2}$ is up to 15 hours. Approximately 95% is excreted unchanged in the urine.

ADVERSE EFFECTS :

Hydrochlorthiazide may be associated with electrolyte imbalances including, hypokalaemia and hypomagnesaemia. Glucose tolerance may be reduced, diabetes precipitated and control with antidiabetic agents lost. Hyperuricaemia may precipitate gout. Blood liproproteins may be adversely affected, resulting in an increase in triglycerides and LDL and a decrease in HDL.

DOSE :

The dose is usually 12.5 - 25 mg daily, as a single morning dose is adequate for blood pressure control

CYCLOPENTHIAZIDE

PHARMACOKINETICS :

Little is known about the extent of absorption, distribution and elimination half-life of cyclopenthiazide. Diuretic action occurs within 1 - 2 hours and lasts for up to 12 hours. It appears to be excreted almost unchanged in the urine.

DOSE :

A dose of 0.25mg as a single daily dose is used for hypertension. In South Africa cyclopenthiazide is only available in combination with potassium chloride.

HIGH-CEILING DIURETICS, SULFONAMIDES

FUROSEMIDE

Furosemide is chemically similar to the thiazide diuretics (BMJ, 1986). Furosemide is a less potent antihypertensive agent than are the thiazide diuretics and is usually used in combination with other antihypertensive agents. Furosemide is mainly used where there is renal impairment and in patients with diabetes.

PHARMACOKINETICS :

Approximately 60 - 70% of the oral dose is absorbed. Onset of action after an oral dose is within 30 - 60 minutes and lasts approximately 3 - 6 hours, but the maximum antihypertensive effect may only be evident after a few days. The plasma $T_{1/2}$ is 1.5 hours, although this may be prolonged in renal or hepatic failure. 60 - 70% is excreted unchanged in the urine and the rest is metabolised in the liver.

ADVERSE EFFECTS :

The most common adverse effects are fluid and electrolyte imbalances (e.g. hypokalaemia, hypomagnesaemia, hypocalcaemia and hypochloraemic alkalosis). Hearing impairment is associated with large doses, especially if combined with

other drugs with ototoxic potential. Sulphonamide-sensitive patients may develop allergic dermatologic and vasculitic reactions.

DOSE :

An oral dose of 20 - 40mg daily are usually sufficient for the management of hypertension.

POTASSIUM-SPARRING AGENTS

SPIRONALACTONE

MECHANISM OF ACTION :

Spironalactone is a competitive inhibitor of aldosterone on the distal tubules. Its hypotensive mechanism is thought to be due to blocking the effect of aldosterone on arteriolar smooth muscle or by altering the extracellular-intracellular sodium gradient.

PHARMACOKINETICS :

About 70% of the oral dose is absorbed and is metabolised, by the liver, to canrenone, which is the major active metabolite (Goodman & Gilman, 1990). The plasma $T_{1/2}$ of canrenone is 10 - 35 hours. Spironolactone and canrenone are excreted predominantly by the kidneys.

ADVERSE EFFECTS :

The most serious side effect is hyperkalaemia as it can cause cardiac irregularities. This is more probable when used with potassium supplements or potassium-sparring agents or in patients with renal failure. Other effects are

anorexia, vomiting, abdominal cramps, diarrhoea, headache, drowsiness, deepening of the voice, hirsutism and confusion.

DOSE :

Spironalactone is usually used in a dose of 25 - 100mg daily.

AMILORIDE/TRIAMTERENE

MECHANISM OF ACTION :

Amiloride and triamterene inhibit the sodium channel, which is concerned with sodium reabsorption in the distal tubule. They are weak diuretics when used alone, but also has some antihypertensive activity. When combined with another diuretic, this effect is additive. Both have potassium and magnesium-sparring properties.

PHARMACOKINETICS :

About 50% of the oral dose of amiloride and triamterene are absorbed. The onset of diuretic activity is within 2 hours and lasts for up to 24 hours with amiloride and 7 - 9 hours with triamterene. The $T_{1/2}$ of amiloride is 6 - 9 hours. Amiloride is not metabolised and is eliminated unchanged by the kidneys whereas triamterene is extensively metabolised in the liver and excreted in the urine (Goodman & Gilman, 1990).

ADVERSE EFFECTS :

The most serious adverse effect is hyperkalaemia, but when combined with a thiazide diuretic this effect is less. Other effects are nausea, anorexia, abdominal pain and flatulence, headache, weakness and dizziness.

DOSE :

Amiloride and triamterene are only available in South Africa in combination with hydrochlorthiazide. When combined with a thiazide diuretic a single daily dose of 2.5 - 5mg of amiloride and 25 - 50 mg of triamterene is used in the management of hypertension.

BETA BLOCKING AGENTS, PLAIN

MECHANISM OF ACTION :

They competitively inhibit the action of catecholamines on beta adrenoreceptors (BMJ, 1984). Some block both B_1 receptors (heart rate and contractility) and B_2 receptors (vascular and bronchial smooth muscle), whereas others block mainly B_1 receptors and are relatively cardioselective. They are thought to reduce the blood pressure by reducing the cardiac output. But with continued treatment cardiac output returns to normal while blood pressure remains low, owing to decreased peripheral vascular resistance (Katzung, 1989).

BETA BLOCKING AGENTS, NON-SELECTIVE

PROPRANOLOL

PHARMACOKINETICS :

The oral bioavailability is low due to first-pass metabolism. Propranolol is lipid-soluble and readily passes across the blood brain barrier. The $T_{1/2}$ is 3 hours, but because propranolol is extensively metabolised in the liver to give

an active metabolite, 4-hydroxypropranolol, the effective half-life becomes much longer.

ADVERSE EFFECTS :

The most common side effect is lethargy and a heavy feeling in the limbs (Burgess, 1991). Effects on the central nervous system can result in nightmares, sleep disturbances and even mild depression. Propranolol frequently causes bradycardia, dizziness, drowsiness, visual disturbances and hallucinations, confusion and mental depression . GI disturbances include nausea, vomiting, diarrhoea and constipation. Sexual dysfunction also occur. HDL lipoproteins are reduced while serum triglyceride levels are increased.

DOSE :

The usual starting dose of propranolol is 20 - 40mg twice daily and may be increased to a dose of 120 - 320mg/ day in 2 divided doses, although there is little additional antihypertensive effect above 80 mg per day.

CARDIOSELECTIVE BETA BLOCKING AGENTS (C07AB)

ATENOLOL

PHARMACOKINETICS :

50 - 60% of the oral dose is absorbed and the plasma $T_{1/2}$ is 6 - 7 hours, but the antihypertensive effect lasts up to 24 hours. Atenolol has poor lipid solubility and therefore does not readily cross the blood brain-barrier. 90% of an oral dose is excreted unchanged in the urine.

ADVERSE EFFECTS :

The most troublesome of the symptomatic adverse effects are cold extremities and fatigue.

DOSE :

The usual dose for hypertension is 50 - 100mg, although atenolol has a flat dose response curve therefore doses above 50 mg daily have little value (BMJ, 1986).

METOPROLOL

MECHANISM OF ACTION :

The mechanism of action of metoprolol is essentially the same as that of propranolol, except for the fact that metoprolol is less potent in blocking B_2 receptors (Katzung, 1989).

PHARMACOKINETICS :

Metoprolol is rapidly and almost completely absorbed after an oral dose. Bioavailability may be increased by food. The plasma $T_{1/2}$ is about 4 hours. About 50% of the drug appears to undergo first-pass metabolism in the liver and only about 10 % is eliminated unchanged in the urine. Metoprolol is rapidly and widely distributed in the body and readily crosses the blood-brain barrier.

DOSE :

The starting dose of metoprolol is 25mg bd which may be increased slowly to a maintenance dose of 100 - 400 mg daily as a single or divided into a twice daily dose (Opie, 1991).

APPENDIX VI

DRUG INTERACTIONS

1. Amiloride Co. / Metformin and Chlorpropamide

By raising blood sugar levels the thiazide diuretics and other related diuretics can reduce the effects of the hypoglycaemic agents and impair the control of diabetes. This effect is well documented but only of minor clinical significance. Concurrent use need not be avoided but the effects should be monitored. Some patients will require a modest increase in their dose.

There is also a report of eight cases of hyponatraemia in patients on *Moduretic* (hydrochlorthiazide 50mg and amiloride 5mg) and chlorpropamide. This interaction is rare and of minor clinical importance (n=3; classified as a minor interaction).

2. Amiloride Co. / Triamterene Co., *Brinerdin* and Rauwolfia Co.

The concurrent use of two potassium sparing / thiazide combinations is unnecessary and will lead to the potentiation of the undesirable effects of the thiazide diuretics (n=5; classified as increased side effects).

3. Amiloride Co. / Carbamazepine

There are two reports of patients an thiazide diuretics who developed symptomatic hyponatraemia while on carbamazepine. Although both drugs can cause sodium loss from the body, one should be aware of the possible potentiation. The interaction is however uncommon and only of minor clinical importance (n=1; classified as a minor interaction).

4. Amiloride Co., Thiazides and Indapamide / Indomethacin and Ibuprofen

The antihypertensive effects of the thiazides and related diuretics can be reduced to some extent by indomethacin. The interaction appears to be of only moderate clinical significance and may possibly only be a transient effect. Ibuprofen appears to interact to a lesser extent or not at all. Concurrent use of the two drugs is not contra-indicated but the patient should be monitored and the thiazide dose adjusted if necessary (n=7; classified as a moderate interaction).

5. **Methyldopa / Digoxin**

Methyldopa does not affect digoxin levels, but marked bradycardia has been observed in two elderly women when given both drugs. Concurrent use need not be avoided but the heart should be monitored for any slowing as this effect seems to be more than the sum of the two individual drugs (n=1; classified as a minor interaction).

6. **Methyldopa / Oxazepam**

This is in fact not a true interaction but more one of additive side effects. Concomitant use of the two drugs could lead to additive depressant effects on the central nervous system e.g. sedation (n=1; classified as increased side effects).

7. **Methyldopa / Phenobarb**

The effects of methyldopa are not altered by the use of phenobarbitone, but once again the central nervous system side effects of each of the drugs will be exacerbated when used together (n=1; classified as increased side effects).

8. Rauwolfia Co. / Methyldopa

Concurrent use of these two drugs will lead to the additive of both of their side effects such as, nasal congestion and sedation(n=1; classified as increased side effects).

9. Rauwolfia Co. / Phenytoin

Concurrent use of these two agents could result in the additive effects of the individual agents side effects such as, drowsiness and depression (n=1; classified as increased side effects).

10. Reserpine / Tricyclic Antidepressants

Rauwolfia alkaloids cause depression and sedation and are therefore not usually used in patients needing treatment for depression (n=1; classified as a moderate interaction).

11. Beta-blockers / Alpha-blockers

Prazosin causes some patients to experience acute postural hypotension, tachycardia and palpitations when they first start treatment. Postural hypotension is more likely to occur if the patient is already taking a beta-blocker. Concurrent use need not

be avoided, but in order to avoid postural hypotension, it has been recommended that patients already taking beta-blockers should start on a low dose of prazosin (n=1; classified as increased side effects).

12. Beta-blockers / Indomethacin and other NSAIDs

Indomethacin reduces the antihypertensive effects of the beta-blockers. This interaction can be accommodated either by raising the dosage of the beta-blocker or by using a non interactive NSAID. The concurrent use of indomethacin need not be avoided but one should anticipate the need to increase the dosage of the beta-blocker. Alternatively exchange the indomethacin with a non-interacting NSAID. Imidazole salicylates, naproxen, ibuprofen and sulindac interact minimally or not at all (n=2; classified as a minor interaction).

13. Diltiazem / Nifedipine

A reduction in the metabolism of the nifedipine by diltiazem has been suggested, although the information is limited and the clinical importance is uncertain
(n=1; classified as increased side effects).

14. Verapamil / Digoxin

The Digoxin-Verapamil interaction is well established and occurs in most patients. Serum digoxin levels should be well monitored and downward adjustments made to avoid digoxin toxicity. A 30 - 50% dosage reduction is recommended. The magnitude of the increase is digoxin levels is dose dependant with a significant increase if the verapamil dosage is increased from 160mg to 240mg daily (n=1; classified as a moderate interaction).

15. ACE Inhibitors / Oral Hypoglycaemics

Hypoglycaemia has been seen in a few diabetics treated with *Captopril* and *Enalapril*. Concurrent use need not be avoided but it would be prudent to warn patients that excessive hypoglycaemia has occurred and it may therefor necessary to modify the dosage of the oral hypoglycaemic agent (n=2; classified as a minor interaction).

16. ACE Inhibitors / Amiloride Co., Triamterene Co. and Thiazide Diuretics

Normally the concurrent use of diuretics and ACE inhibitors is safe and effective but hypotensive symptoms occasionally occur. Potassium sparing diuretics such as amiloride, triamterene or potassium supplements can result in hyperkalaemia and should not

be used in conjunction with ACE inhibitors unless the serum potassium levels can be monitored, although there is some evidence to suggest that this effect is less marked with *Enalapril* than with *Captopril* (n=8; classified as a minor interaction).

APPENDIX VII

THE PRICE OF DRUGS IN THE PUBLIC AND PRIVATE SECTORS

SINGLE DRUGS

GENERIC NAME	PRICE (in cents/tablet) PUBLIC	PRIVATE
Atenolol 50 mg	12.9	116.9
100 mg	22.4	179.2
Captopril 25 mg	30.3	192.5
50 mg	67.7	315.9
Diltiazem 60 mg	43.0	184.3
90 mg	56.4	304.0
Enalapril 5 mg	32.2	199.7
10 mg	58.9	281.7
20 mg	135.5	410.6
Furosemide 40 mg	2.3	35.0
Hydralazine 25 mg	2.2	42.5
Hydrochlorothiazide 25 mg	1.2	54.1
Indapamide 2.5 mg	13.5	215.9
Lisinopril 5mg	not available	175.1
10mg	not available	246.8
20 mg	not available	410.6
Methyldopa 250 mg	8.9	39.0
Metoprolol 100 mg	36.0	269.8
Nifedipine 10 mg	19.6	96.8
Prazosin 1 mg	8.2	59.9
2 mg	14.0	100.2
5 mg	31.2	238.9
Propranolol 40 mg	1.8	41.6
Ramipril 2.5 mg	27.4	208.4
5 mg	54.9	310.9
Reserpine 0.25 mg	1.1	3.3
Spironolactone 25 mg	5.3	48.8
Verapamil 40 mg	4.0	58.8
80 mg	7.1	84
120 mg	12.0	103.5

COMBINATION DRUGS

TRADE NAMES	PRICE (in cents/tablet) PUBLIC	PRIVATE
Aldazide [R] Spironalactone 25 mg IsobutylHCTZ 2.5 mg	not available	175.7
Brinerdin [R] Dihydroergocristine 0.5 mg Clopamide 5 mg Reserpine 0.1 mg	18.3	321.8
Co-reitec [R] Enalapril 20 mg Hydrochlorothiazide 12.5 mg	not available	533.3
Dyazide [R] Triamterene 50 mg Hydrochlorothiazide 25 mg	7.1	67.0
Moduretic [R] Amiloride 5 mg Hydrochlorothiazide 50 mg	2.4	52.7
Navidrex - K [R] Cyclopenthiazide 0.25 mg KCL 600 mg	4.8	105.3
Protensin- M [R] Hydroflumethiazide 50 mg Reserpine 0.125mg	not available	62.6
Rautrax -25 [R] Hydroflumetiazide 25 mg Rauwolfia serpentina 50 mg KCL 625 mg	9.8	90.9
Urex - K [R] Hydrochlorothiazide 50 mg KCL 300 mg	not available	29.4