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**LA THÈSE A ÉTÉ
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SINGLE EVENING VERSUS MULTIPLE DOSING
REGIMENS OF METHYLDOPA

BY

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Thesis presented to the School of
Graduate Studies in partial fulfillment
of the requirements for the degree of
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ABSTRACT

The effectiveness of single and multiple dosing regimens of methyldopa and the incidence of side effects with these two regimens were compared in a double-blind, crossover trial. Eight patients were included in the study analysis. Four patients were in treatment schedule A which consisted of a 4-week period of methyldopa three times daily, followed by 4 weeks of methyldopa, total dose at bedtime, and 4 patients were in treatment schedule B which consisted of the reverse sequence. Blood pressure determinations were done, one day a week, in the morning and in the evening, in the sitting, standing and supine positions. The results indicated that single dosing of methyldopa further decreased the baseline blood pressure in the sitting and standing positions and maintained the supine baseline blood pressure. The incidence of side effects was not significantly different with both regimens. It is possible to recommend a single evening dose regimen of methyldopa for some patients previously maintained on a multiple dose regimen. This simplified regimen might encourage patient compliance.

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LIST OF ABBREVIATIONS

AM	-morning
PM	-evening
mmHG	-millimetre of mercury
TID	-three times daily
HS	-at bedtime
DOPA	-dihydroxyphenylalamine
mg	-milligram
SL	-sublingual
PRN	-as needed
tbsp	-tablespoonful
qid	-four times daily
S.E.M.	-standard error of the mean
df	-degree of freedom
ss	-sum of squares
ms	-mean sum of squares
PRA	-plasma renin activity

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INTRODUCTION

Hypertension belongs to the most frequently occurring diseases at present. In view of the high incidence of hypertension and its particularly dreaded complications, there remains little doubt that adequate treatment is desirable. Despite the availability of effective antihypertensive agents, there still remains a high portion of inadequately treated hypertensive patients. Many patients, due to the asymptomatic nature of the disease in its early stages, find it difficult to comply with a drug regimen that disrupts their daily routine and, more importantly, that produces unwanted side effects. Recent efforts to improve the management of hypertension have focussed on simplifying the drug regimen for these patients and minimizing undesirable side effects.

Methyldopa is an effective antihypertensive agent, which became commercially available in 1964 and which is still one of the most widely used antihypertensive drugs. Since this drug is usually given three to four times a day, the feasibility of simplifying the dosing administration of methyldopa was investigated. Also, since sedation is one of the more common side effects of methyldopa, it was hypothesized that a single bedtime dosing schedule with methyldopa would simplify the regimen and would minimize this associated side effect.

CHAPTER I

REVIEW OF THE LITERATURE

For a large proportion of hypertensive patients, the cause of this increased blood pressure remains unknown. However, the serious complications associated with this sustained high blood pressure and the importance of therapy are well documented and will be reviewed.

Although a single cause of hypertension has not been defined, several factors, including alterations of the regulators of normal blood pressure, have been implicated. A review of these etiologic factors demonstrates that many of the pharmacological agents presently used in the management of hypertension are aimed at correcting one or several of these factors.

Various classifications of drugs have proven effective in lowering blood pressure and the antihypertensive efficacy of methyldopa, in particular, will be reviewed.

Adequate management of a chronic disease does not depend, however, on the sole availability of effective therapeutic agents. A review of the problems associated with long-term management of hypertension is therefore provided to demonstrate the work that still must be done in an attempt to individualize and improve therapy.

Only a highlight of the extensive literature on hypertension can possibly be provided but this review will attempt to focus on the specific issues mentioned previously.

I. NATURE OF THE DISEASE

A large proportion of the Canadian population have uncontrolled hypertension. Data from the Nutrition Canada Survey¹ indicate that 12.5 per cent of men and 11.2 per cent of women in Canada have uncontrolled hypertension, when using a diastolic pressure of 100 mm Hg as the cut off point. In Ontario, similar figures were obtained, namely 9.8 per cent of men and 8.9 per cent of women had uncontrolled hypertension. However, each of these reports resulted from a single set of casual blood pressure measurements. Since approximately one-third to one half of those individuals who are found to be hypertensive on a first examination will revert to normal blood pressure on repeat examination,² these reports probably overestimate the frequency of hypertension. Nonetheless, a large number of Canadians have uncontrolled hypertension.

Despite the fact that at any given time, the majority of people with hypertension are asymptomatic, they are nonetheless at a greatly increased risk of experiencing strokes,^{3,4} coronary artery disease⁵ and heart failure.⁶ When hypertension coexists with other

major risk factors, such as cigarette smoking and hypercholesterolemia, the risks are additive.⁷ In all these studies, it is clear that blood pressure elevation of any degree will increase the risk of cardiovascular disease but the risk increases much more when blood pressure exceeds the arbitrary norm of 140 mm Hg systolic and 90 mm Hg diastolic.

However, these studies, in which blood pressure level is related to the risk of cardiovascular disease and death, do not answer the question of whether antihypertensive drugs have a favourable benefit versus risk ratio. The answer emerges from a review of randomized clinical trials in which homogeneous groups of hypertensives, who had been randomly assigned to receive either active antihypertensive drugs or inert placebos, were kept under continuous, close observation for the subsequent occurrence of the complications of hypertension.

The clinical efficacy of antihypertensive therapy in decreasing morbidity and mortality was most readily established for severe hypertension where the cardiovascular risk was very great.⁸⁻¹⁰ Although these studies were not randomized clinical trials, any reduction in the higher death rate seen in untreated malignant hypertension was considered to be clinically significant.

Only recently has the value of therapy been proven for less severe degrees of hypertension. In a

randomized trial of patients with a diastolic blood pressure between 115 and 130 mm Hg anti-hypertensive therapy significantly lowered the incidence of hypertensive complications and improved survival as compared to placebo.¹¹ However, the accelerated rate of development of atherosclerotic coronary artery disease had not been slowed and the incidence of sudden death had not been clearly changed by therapy.

Similar results have been reported for patients with diastolic pressure between 90 and 114 mm Hg.¹² Treatment was beneficial but risk reduction was less among subjects with less severe hypertension and was not statistically significant for all groups. Indeed, for the patient with a diastolic pressure between 90 and 104 mm Hg, the data indicated that the greatest benefit was seen in those who already had cardiovascular-renal abnormalities which included many patients over 50 years of age.¹³ Furthermore, clear-cut risk reduction occurred even if diastolic pressure could not be lowered all the way to goal (less than 90 mm Hg).¹⁴ A recent trial of the Hypertension, Detection and Follow-up Program studied more intensely the effect of treatment in patients with diastolic blood pressures between 90 and 104 mm Hg.³⁰² This trial represents a 5-year follow-up in 11,000 patients in 14 medical centres across the United States. Among the intensely treated patients with mild hypertension, the 5 year mortality from all causes was 20 per cent lower and cardiovascular mortality was 26 per cent lower. It clearly demonstrated that early systematic and aggressive treatment of hypertension in this group significantly reduces mortality from hypertension-associated cardiovascular disorders.

The treatment of hypertension did not affect stroke recurrence, although it was useful in preventing heart failure among women and

congestive heart failure among patients with initial diastolic blood pressures between 100 and 115 mm Hg.¹⁵

Similar to the results of the Veterans' Administration trials,¹¹⁻¹³ the difference in outcomes of the treated group and the placebo group in a controlled study done in Baltimore was significant and, among the black women, highly statistically significant.¹⁶ The analysis grouped all initial diastolic blood pressures in the range of 100 to 130 mm Hg.

All these randomized clinical trials have shown that the treatment of hypertension prevents or delays many of the complications of hypertension, and that treatment is warranted in that subgroup of patients that can most benefit from therapy.

2. REGULATION OF BLOOD PRESSURE

Arterial pressure is equal to the product of the cardiac output and peripheral resistance. The control of cardiac output is an interplay of cardiac function and of the venous capacitance and blood volume, whereas the control of peripheral resistance occurs at the arterioles.¹⁷ Physiologic control of pressure is exerted at these sites by several important reflex regulatory mechanisms that operate through the autonomic nervous system and the renin-angiotensin-aldosterone system.

2.1 Autonomic nervous system

The relative importance of the several ways in which the autonomic nervous system contributes to blood pressure control is unknown. One of the important regulatory mechanisms of blood pressure that has been described is the vasoregulatory reflex arc which functions by a negative feedback mechanism.¹⁸ The principal baro-

sensory areas are localized in the heart, carotid sinus, aortic arch and in other large vessels. These sensory receptors are activated by local distension produced by an increase in blood pressure. The information is relayed through a system of afferent fibres to the central nervous system to inhibit the tonic activity of the vasomotor centres which, in turn, modulate the peripheral cardiovascular system by means of an efferent network of sympathetic and parasympathetic fibres. The efferent parasympathetic component is made up of a network of inhibitory fibres distributed mainly to the heart and to selected vascular beds which are thought to be hemodynamically insignificant. However, certain experiments,^{19,20} have revealed that the influence of the parasympathetic system is at least as important as the sympathetic tone in the regulation of cardiac output. In contrast, the efferent sympathetic fibres are more closely related to the cardiovascular system by a dense plexus of excitatory fibres distributed to the heart and to all vascular beds, with the exception of intracerebral vessels. The contribution of noradrenergic mechanisms to normal cardiovascular homeostasis is plausible considering the presence of noradrenergic fibres and receptors at various critical points along the cardiovascular reflex arc. At the baroreceptor level, numerous noradrenergic fibres have been demonstrated.²¹ Although their exact role is still unknown, it is possible that the activity of these fibres could modulate the

sensitivity of the baroreceptors. At the central level, cardio regulatory and vasomotor centres are densely innervated by adrenergic fibres.²² Moreover, the intermediolateral horn of the spinal cord, which is the origin of the preganglionic sympathetic neuron, is also innervated by noradrenergic and serotonergic fibres.²³ The discovery that several drugs are producing their hypotensive effect through an action on central noradrenergic fibres has brought new insight into the understanding of the role of these fibres. In the periphery, the great majority of postganglionic sympathetic fibres are noradrenergic. With the histo-fluorescence technique, the distribution of these fibres has been visualized in a variety of vascular beds.^{24,25} Small arterioles, which are crucial in the maintenance of blood pressure homeostasis,¹⁷ were found to be the most densely innervated segments of the vascular tree. In addition to this network of fibres, the sympathetic system is also responsible for the control of catecholamine secretion by the adrenal medulla.²⁶ Since the heart and blood vessels contain specific receptors to catecholamines,²⁷ these structures can therefore be influenced either by noradrenaline liberated from the sympathetic nerve endings or by catecholamines secreted by the adrenal medulla into the circulation. It thus appears that abnormalities in adrenergic mechanisms at various critical points along the cardiovascular reflex arc could impair the equilibrium and stability of this

regulatory mechanism.

The role of the sympathetic system in the control of cardiovascular functions has been studied by several investigators but results have often been conflicting due, in great part, to the problem of achieving specific and extensive sympathectomy using surgical denervation, immuno-sympathectomy or noradrenaline depleting agents. The use of 6-hydroxydopamine (6-OHDA) has permitted a better evaluation of the relative role of the sympathetic fibres and the adrenal medulla in the regulation of blood pressure and cardiac functions in normal animals. Studies using this compound as a means to produce generalized sympathectomy²⁸⁻³⁰ found that under basal conditions, the sympathetic fibres are mainly responsible for the maintenance of cardiovascular functions, whereas the adrenal medulla contributes little to these functions. However, it appears that the adrenal medulla can play an important compensatory role in the maintenance of cardiovascular functions in sympathectomized animals. After destruction of the sympathetic fibres by 6-OHDA, the release of catecholamines by the adrenal medulla is markedly increased so that the sympathetic tone on the cardiovascular system can be partially maintained, indirectly by the action of circulating amines.^{29,30} In the absence of both components of the sympathetic system, the cardiovascular functions could not be sustained at viable levels, thus indicating the importance of the sympathetic system for their maintenance.

Autonomic insufficiency and the consequences of cardiac transplantation are clinical models that emphasize the importance of the autonomic nervous system in the normal function of the cardiovascular system. Autonomic insufficiency results in a syndrome consisting of orthostatic hypotension with syncopal episodes, a slow pulse rate, impaired glucose mobilization, bowel and bladder dysfunction, impotence and abnormalities of sweating. The syndrome can be caused by a variety of diseases affecting the central or peripheral autonomic nervous system.

2.2 Renin-angiotensin system

As indicated previously, blood pressure regulatory mechanisms are also thought to operate through the renin-angiotensin-aldosterone system. In 1934, Goldblatt demonstrated renal mechanisms of blood pressure control by producing hypertension in the dog, by clamping the renal artery.³¹ This experiment suggested the release of a pressor substance from the kidney, when its circulation was impaired. Since that time, a cascade of enzymes, peptide and steroid hormones and cofactors belonging to the renin-angiotensin-aldosterone system have been identified and characterized but the exact contribution of renin and angiotensin to the maintenance of blood pressure and volume homeostasis in the normal person has not yet been fully defined.

Angiotensin II is the principal effector hormone

of the renin-angiotensin-aldosterone system. It has a major role in maintaining circulatory homeostasis in the normal animal through its direct effects on arteriolar smooth muscle and its aldosterone-stimulating effects. Studies using peptide inhibitors of angiotensin I-converting enzyme and specific competitive inhibitors of angiotensin II have helped to define that role. In the normal animal on a normal salt intake, angiotensin II is not required for the acute maintenance of blood pressure.³²⁻³⁶ In a variety of conditions that stress the renin-angiotensin system, such as salt depletion,^{32,37,38} diuretic administration,³² and thoracic caval constriction,³⁵ acute administration of a converting enzyme inhibitor or an angiotensin II-blocker lowers blood pressure and causes a rise in plasma renin activity. Probably because of blockade of angiotensin II receptors, aldosterone secretion is decreased.^{35,38} The fall in blood pressure and the rise in renin activity after administration of a converting enzyme inhibitor increase with progressive volume depletion induced by a diuretic.³² Blockade of angiotensin I-converting enzyme does not interfere with postural homeostasis in normal man on a normal salt intake, but does lead to postural hypotension in salt-deprived man.³⁹ It would therefore seem that the renin-angiotensin system, acting through angiotensin II, is required for the maintenance of blood pressure in the presence of volume depletion in the normal animal and in normal man.

The renin-angiotensin system has been related to adrenergic vascular control mechanisms, to the prostaglandins,^{40,41} and to the kallikrein-kinin system. The precise cellular mechanisms governing renin release are as yet speculative. Both changes in renal perfusion pressure and either concentration or amount of sodium in the distal tubule have a regulatory effect. The effects of blood pressure, blood volume, posture and sodium intake on renin release are probably mediated by one of these variables.⁴²⁻⁴⁴

3. PATHOGENESIS OF HYPERTENSION

The known effects of the autonomic nervous system and that of angiotensin on blood pressure have stimulated interest in the possible roles of deranged functioning of these systems in the pathogenesis of human hypertension. Certain forms of secondary hypertension, such as pheochromocytoma and renal hypertension, have been attributed to disorders of the sympathetic nervous system and the renin-angiotensin system, respectively. These forms of hypertension are classified as secondary hypertension and often by surgical intervention, they can be cured. However, the role of these systems in the etiology of essential hypertension, only, will be reviewed at this time. As the name suggests, essential hypertension implies that the cause is unknown. This form of hypertension accounts for 80 per cent or more of all hypertensives. Although it is suggested that the autonomic nervous system and the renin-angiotensin system play a large role in the pathogenesis of

essential hypertension, other etiological factors have also been shown to be contributive and will also be reviewed.

The fundamental factor in the pathogenesis of essential hypertension is an increased peripheral resistance,⁴⁵ coupled with normal or decreased cardiac output or blood volume or both.⁴⁶ The extracellular fluid volume has been found within normal limits in patients with essential hypertension.^{47,48} It has recently been suggested that the initial increase in cardiac output does not seem to be an essential factor in the maintenance of borderline hypertension.⁴⁹ There is overwhelming evidence that the increased peripheral resistance in the early stage of human essential hypertension is functional and leads eventually to organic wall changes and a decrease in the ratio of wall to lumen,^{5,50,51} although it cannot be ruled out that the total number of arterioles may be reduced as occurs in spontaneous hypertensive rats.⁵² The functional nature of the increased peripheral resistance in essential hypertension is manifested by an increased sensitivity and responsiveness to norepinephrine⁵³ and angiotensin II.⁵⁴ This increased sensitivity which was observed in most forms of experimental hypertension and in human hypertension was first interpreted as an indirect indication that the sympathetic system might be involved in the etiology and maintenance of hypertension.⁵⁵ However, the exact significance of these changes in vascular sensitivity has not been defined. The observation that the hypersensitivity is not

specific to norepinephrine suggests that the mechanism underlying the phenomenon may be unrelated to adrenergic nerve function. It has been proposed that the thickening of the arterial wall resulting in an increased wall-to-lumen ratio was responsible for the increased sensitivity to pressor agents. But it has also been argued that this phenomenon may not be due simply to anatomical changes of the arterial wall since increased reactivity is not observed in all vascular beds in patients with essential hypertension.⁵⁶ It has been hypothesized that these changes in arterial functioning are related to an excessive sodium intake in genetically-predisposed individuals⁵⁷ or to a primary and mild hypermineralocorticoid activity^{58,59} and that this would lead to an alteration in membrane permeability⁶⁰ and changes in contents or ratios of cations of arterial smooth muscle cells, producing in turn an increased resting basal tonicity and hypersensitivity and hyper-responsiveness of the contractile proteins to norepinephrine and angiotensin II. Whatever the mechanisms involved, it remains that, in the presence of increased vascular reactivity, normal circulating catecholamines and normal sympathetic activity could contribute significantly to the maintenance of an elevated blood pressure in hypertension.

To date, no one has clearly demonstrated consistently higher plasma concentrations of either norepinephrine or angiotensin II in patients with early and mild essential hypertension, when matched for age, race and sex

with groups of control subjects.⁶¹ Studies using double isotope labels have revealed an increase in plasma catecholamines in essential hypertension in several different laboratories⁶²⁻⁶⁵ and no change from the normal in another.⁶⁶ Plasma dopamine beta-hydroxylase levels, which are usually a measure of sympathetic activity,⁶⁷⁻⁶⁹ have been found to range widely in normotensive as well as in essential hypertensive subjects.⁷⁰ In addition, it has been demonstrated that stress increases the blood pressure and the excretion of catecholamines in the urine more in hypertensive than in normotensive subjects,⁷¹ although this relationship is disputed by others.⁷² It is also well known clinically that the essential hypertensive subject responds to drugs affecting the sympathetic nervous system such as reserpine, methyldopa or guanethidine, with a greater decrease in blood pressure than does the normotensive subject.⁷³ Many of these relationships remain controversial and many of the discrepancies can probably be attributed to differing methodologic factors. Methodologic improvements in the measurements of catecholamines and their metabolites may allow some of these issues to be resolved in the future.

The involvement of the renin-angiotensin system in the pathogenesis of essential hypertension has not been defined. However, a heterogeneity of plasma renin values in essential hypertension may be of pathophysiologic and prognostic importance. One study⁷⁴ indicates that the rate

of cardiovascular complications in a series of 219 patients with essential hypertension was zero in the low renin group, 11 per cent in the normal renin group and 14 per cent in the high renin group over a 10-year follow-up period. Groups with low and normal renin had similar mean diastolic blood pressures; the high renin group had a higher mean diastolic pressure. The low renin group was older and contained more black patients (42 per cent blacks in the low renin versus 24 per cent in the normal renin and 11 per cent in the high renin group) than the other two groups. These data led to a hypothesis that plasma renin levels are related to natural history and prognosis in essential hypertension. It was postulated that elevated renin activity is a risk factor in essential hypertension, that low renin essential hypertension may have a distinctive pathophysiology and a more benign natural history, that renin levels may be used as therapeutic guides in essential hypertension, and that correction of renin abnormalities as well as blood pressure elevations may be a worthy therapeutic goal. Analysis of retrospective data by an additional group⁷⁵ has also suggested the possible reciprocal relation between plasma renin activity and frequency of cardiovascular complications in essential hypertension although differences between the two groups were small. Five other groups have found no such relationship.⁷⁶⁻⁸⁰ None found a decreased rate of cardiovascular complications in the low renin group as compared with either the normal

renin or a composite of the groups with normal and high renin. It was also observed that plasma renin activity did not correlate with the frequency of vascular complications in a group with treated essential hypertension.⁷⁷ These studies therefore call into question the prognostic value of plasma renin activity in either untreated or treated patients with essential hypertension. Possibly in support of the contributory role of renin in the pathogenesis of essential hypertension is the fact that captopril, a converting enzyme inhibitor which prevents the transformation of inactive angiotensin I into active angiotensin II, has been shown to reduce the arterial pressure not only in patients with renin-dependent hypertension but also in those with essential hypertension.^{81,82} The careful prospective studies that are needed either to substantiate or to refute the pathophysiologic role of renin in essential hypertension have yet to be performed.

4. OTHER ETIOLOGIC FACTORS

4.1 Heredity

The concept that genetic factors play an important role in blood pressure regulation is well established in the literature. After reviewing eight family studies, some based on history, some on blood pressure measurement and some on diagnostic examination, Schweitzer et al concluded that each was consistent with the hypothesis of familial aggregation in essential hypertension.⁸³ However, families share their environment as well as their genes such that demonstration

of familial correlations does not necessarily require the operation of genetic influences.

More recent studies provide more direct evidence for the important role of heredity in blood pressure regulation. First of all, Zinner et al observed the phenomenon of familial aggregation in essential hypertension among the young children from natural families.⁸⁴ Biron et al confirmed this observation for natural but not adopted children and concluded that "familial aggregation of blood pressure, whether between parent and child, or between children is almost entirely the result of heredity."⁸⁵ Finally, further support comes from studies of twins,⁸⁶⁻⁸⁸ the most definitive one involving comparisons of monozygous and dizygous twins.⁸⁹ Monozygotic twins showed higher correlations for both systolic and diastolic pressures than other relatives. Thus, there emerges a clear picture of a major genetic determination of arterial blood pressure and of hypertension as defined at various levels.

4.2 Salt intake

There is considerable evidence suggesting that excess ingestion of salt is involved in the genesis of essential hypertension. In man, the evidence is indirect but in the laboratory animal, the evidence is direct and unequivocal.^{91,92} The evidence supporting the proposition that essential hypertension may be prevented by the elimination of salt from the diet has been the subject of recent reviews.^{93,94} This evidence is both epidemiologic

and experimental. The former consists of studies of unacculturated peoples in whom the prevalence of hypertension is inversely correlated with the level of salt intake.⁹⁵ When unacculturated peoples who are free of hypertension migrate and adopt modern ways of life, blood pressure rises and the complications of hypertension appear. This is invariably accompanied by a sharp rise in consumption of salt. Other environmental factors, including social, economic and other dietary elements, also change but the increase of dietary salt is invariable and appears to be the most important.

The experimental studies consist of a variety of investigations, from demonstrations that restriction of salt in the diet can reduce hypertension^{96,97} to hemodynamic studies suggesting that hypertension is a homeostatic response to a chronically expanded extracellular fluid volume.^{98,99} Also included is the extensive research based on the hypertension-prone laboratory rat model.^{91,92,100} Although the mechanism is as yet inadequately defined, the cause and effect relationship between salt and hypertension in the animal model is unequivocal, such relationship being both direct and quantitative. Moreover, the predisposition to spontaneous or salt-induced hypertension in rats is inherited.

4.3 Obesity

The correlation of blood pressure with obesity is consistent in community as well as clinical settings, and

in observational as well as experimental studies. This positive association is true for adult men and women and for children and has been confirmed in such diverse residential populations as Framingham,^{I01} Tecumseh,^{I02} and Wales,^{I03} as well as in cohorts from steel mill workers,^{I04} aviators^{I05} and college students.^{I06} However, obesity is clearly neither a necessary nor a sufficient cause for hypertension since many obese individuals, including some extremely fat persons, are not hypertensive.

The association of obesity and hypertension is manifested in three different ways: (1) overweight is more prevalent in hypertensive than in normotensive individuals;^{I02,I07-I09} (2) normotensive obese subjects are more likely to become hypertensive;^{I10} and (3) hypertensive subjects are at increased risk of becoming overweight compared to normotensive individuals. Moreover, obesity is associated with a demonstrably increased risk of developing hypertensive cardiovascular complications.^{I08} Relative weight, defined as observed weight over ideal weight for age, sex and race, is one of the descriptive variables which has been found to contribute independently to the future development of hypertension in both cross-sectional and prospective studies.^{I12} In adults, the rate of increase of body weight seemed important, with similar trends noted in children and adolescents.^{I13,I14} This contribution of weight loss to blood pressure control was recently re-emphasized.^{I15}

4.4 Cadmium intake

Hypertensive adults have been reported to have more renal cadmium than normotensive individuals. Chronic low-level cadmium ingestion can induce hypertension in rats. The renal cadmium levels of such rats are comparable to those of the average adult American.^{II6} On the other hand, clinically normal subjects from areas of high cadmium pollution in Sweden and Japan show little evidence of excess hypertension.^{II7, II8} Such data suggest the possibility of a relationship of cadmium and human hypertension which must be considered inconclusive at present.

4.5 Water hardness

A statistical association exists between cardiovascular mortality and mineral content of drinking water. The softer the water, the higher the death rate.^{II9} There does not, however, appear to be a universal relationship with one particular form of cardiovascular disease, the mechanism involved somehow being shared by ischemic heart disease, cerebrovascular disease and hypertensive heart disease. -- Correlations with hypertension without heart disease have not been notable. However, a study involving 12 towns in England and Wales found a higher percentage of sudden death in towns using soft water than in towns using hard water.^{I20} It was also noted that hypertension was more frequently cited in death certificates as a contributing cause in ischemic heart disease deaths in towns using soft water. Diastolic blood pressures were

found to average 2.8 mm Hg higher in these towns. These pilot studies suggest interesting hypotheses for further study, but, for the present, the relationship of water hardness to hypertension is circumstantial and inconclusive.

4.6 Age

With the exception of a number of isolated communities, the list of which includes New Guinea highlanders, Kalahari bushmen, Pacific islanders, South American indians, Australian aborigines, and nomadic tribesmen in East Africa and Mongolia, the gradual rise of blood pressure with age is universal and is associated with cardiovascular complications. Such variations in prevalence and severity as have been observed will ultimately be explained on the basis of interaction of already known and perhaps currently unknown environmental factors at work on a hereditary substrate.

4.7 Psychosocial factors

Aside from the well known differences between blacks and whites in the prevalence of and rate of death from hypertension, the urban-rural differences in deaths due to hypertension in Illinois whites,¹²¹ and the urban-rural gradients in blood pressure noted in Mississippi blacks,¹²² studies to date have not demonstrated consistent or significant differences in prevalence rates for hypertension or hypertensive heart disease ascribable to psychosociologic variables. Occupation, education, income, years of residence in the community, measure of "social

discontinuity" and personality factors have all been examined in unsuccessful attempts to discern meaningful patterns in the variations of blood pressure.

Although it has been previously suggested that different forms of stress are associated with hypertension,^{123,124} the exact nature and importance of this relationship has not yet been clearly defined.¹²⁵ Elevations of blood pressure produced by emotional stress may be related to the subsequent development of sustained hypertension in animals.¹²⁶ Exposure to stress of various kinds has been reported to cause a greater increase in systemic arterial pressure in hypertensive than in normotensive subjects.^{71,72,127} More definitive studies in this area are required before the importance of psycho-cultural factors, including stress, can be assessed.

5. PHARMACOLOGIC MANAGEMENT OF HYPERTENSION

Since no single cause for the maintenance of elevated blood pressure has been identified, many of the pharmacological agents presently used in the management of hypertension are aimed at correcting one or several of the factors implicated in the pathogenesis of essential hypertension. A review of the antihypertensive drugs is presented in such a way as to illustrate the manner in which these drugs influence the various control mechanisms of blood pressure regulation.

As mentioned previously, the sympathetic nervous system seems to play an important role in blood pressure

regulation. However, there is no confirming evidence that it is definitely an etiological factor of essential hypertension. Drugs that interfere with the function of the sympathetic nervous system can effectively lower arterial pressure. However, most of these sympatholytic drugs also affect other etiologic factors, all of which seem to contribute to the final blood pressure lowering effect. Drugs such as reserpine, guanethidine and methyldopa were probably the first agents to be developed and studied.

5.I Reserpine

Reserpine depletes stores of catecholamines and 5-hydroxytryptamine in many organs, including the brain, myocardium, blood vessels and adrenergic nerve endings. Most of its pharmacological effects have been attributed to these actions. I28-I30

It has been shown that reserpine interferes with intracellular storage of catecholamines, but the amounts of reserpine in the tissues are too small for a stoichiometric displacement. It is believed that reserpine competitively inhibits the uptake of dopamine by the chromaffin granules. Evidence of this effect is shown by the failure to release the enzyme dopamine beta-hydroxylase when norepinephrine is released. Normally, dopamine is taken up by the chromaffin granules and hydroxylated to norepinephrine by dopamine beta-hydroxylase. When the catecholamines are released, dopamine beta-hydroxylase is also lost, indicating release from the granule pool; with

reserpine, there is no dopamine beta-hydroxylase released indicating catecholamine release from a cytoplasmic pool.^{I31} Blockage of dopamine uptake by the chromaffin granules may also be the mechanism in which reserpine causes decreased synthesis of norepinephrine. Although there is an effective depletion of norepinephrine, there is an increase in tyrosine hydroxylase activity and an increase in norepinephrine turnover associated with chronic reserpine administration. This is thought due to the increased compensatory firing of adrenergic nerves after reserpine. Furthermore, the depletion of catecholamines by reserpine has been shown to be at least partially dependent on nerve activity and can be reduced by spinal cord section or ganglionic blockade.

Studies with isotopic labelled reserpine show that it is not released by nerve activity even after eighteen hours, when some of the drug has become reversibly bound. Reserpine that remains after 24 to 30 hours is firmly bound and may persist for many days.^{I32}

There is evidence that reserpine has other actions. Reserpine reduces the overall uptake of catecholamines by adrenergic neurons. It has been assumed that this leaves more free agonist to react with tissue receptors and may account for the supersensitivity to catecholamines produced by the drug. Though altered nerve uptake may contribute to the supersensitivity to catecholamines, it has been shown that the overall rate of termination of the action of norepinephrine is not decreased by reserpine and the supersen-

sitivity phenomenon is probably due to other actions.^{I33}

5.2 Guanethidine

Guanethidine is an adrenergic blocking agent with a selective action at the peripheral sympathetic neuron. The selective action results from the fact that guanethidine is a substrate for the adrenergic neuron "norepinephrine pump" that actively transports the drug into the nerve ending where it has its pharmacologic action. In the nerve ending, the drug binds to the storage vesicles and releases norepinephrine from these vesicles.^{I34-I36} Guanethidine not only depletes the nerve endings and myocardium of catecholamines, it also blocks the release of catecholamines normally produced by nerve stimulation. The catecholamines of the adrenal medulla are not affected.

The inhibition of sympathetic function by guanethidine results in hypotension, both orthostatic and supine, by decreasing cardiac output and blunting the responsiveness of the peripheral vasculature and venous capacitance vessels to sympathetic stimulation.

5.3 Methyldopa

Methyldopa is an inhibitor of L-aromatic amino acid decarboxylase and interferes with the decarboxylation of both dihydroxyphenylalanine (dopa) and 5-hydroxytryptophan, thereby reducing the levels of 5-hydroxytryptamine, dopamine and norepinephrine. This occurs in the peripheral and central nervous system. Originally, methyldopa was felt to exert its hypotensive effect by blocking decarboxy-

lation in the sympathetic nerve endings, thereby reducing levels of norepinephrine and resulting in loss of vasomotor tone. Discovery that norepinephrine depletion was not correlated either with the period of decarboxylase inhibition or the degree of the hypotensive response quieted enthusiasm for this theory.¹³⁷

In its place was substituted the "false neurotransmitter" concept. Carlsson and Lindqvist reported the presence of alpha-methylnorepinephrine in the brains of mice and rabbits given large doses of alpha-methyldopa.¹³⁸ However, this compound could not be identified in the urine of hypertensive patients treated with alpha-methyldopa. Sjoerdsma and co-workers also favored this "false transmitter" theory since the metabolite, alpha-methyldopamine, could be recovered in the urine.¹³⁹ These studies therefore led to the hypothesis that the hypotensive mechanism of alpha-methyldopa was mediated by a peripheral "false neurotransmitter." This hypothesis was based upon the knowledge that methyldopa is metabolized to alpha-methylnorepinephrine which can be stored in sympathetic nerve endings thereby displacing norepinephrine and resulting in the release of a false adrenergic neurotransmitter.¹⁴⁰ However, later studies, one of which showed that alpha-methylnorepinephrine is released readily in sympathetic neuroactivity and usually is an effective vasoconstrictor,^{139,140} cast doubt on the "false transmitter" theory. In anesthetized dog and rat, alpha-methylnoradrenaline and noradrenaline had equipotent

pressor activity.¹⁴¹ "False neurotransmission" mechanism would seem to demand that the substance released by the peripheral sympathetic nerves have a lesser vasopressor activity than noradrenaline for which it substitutes. Furthermore, it has been shown that the administration of a peripheral dopa-decarboxylase inhibitor abolishes the synthesis of alpha-methylnoradrenaline without preventing the blood pressure lowering effect of orally administered methyldopa in animals.¹⁴² It would seem therefore that the "false transmitter" concept alone does not explain entirely the antihypertensive effect of methyldopa.

Though impairment of peripheral sympathetic function of methyldopa does not seem by itself of sufficient magnitude to account for its antihypertensive effect, some contribution of peripheral mechanisms cannot be ruled out. It has been suggested that methylnoradrenaline may produce vasodilatation through peripheral beta-adrenergic activity.¹⁴³ Also, it has been reported that methyldopa produces an effective blood pressure lowering effect in immunosympathectomized rats, indicating some direct peripheral action.¹⁴⁴ Finally, postural hypotension is an occasional side effect of methyldopa and it indirectly suggests a peripheral activity.

On the other hand, the drowsiness observed in the initial days of treatment with methyldopa seems to suggest a central mechanism of action. Other side effects such as depression and its effect on lactation also provide

indirect evidence of a central action. These observations seem to indicate that, minimally, methyldopa can penetrate the central nervous system. Jaju and co-workers, in 1966, were the first workers to show that small doses of alpha-methyldopa given centrally to dogs caused a transient fall in blood pressure.¹⁴⁵ This was followed by other studies providing further evidence for a central mechanism of depressor activity.^{146,147} Also in support of the central theory, it was shown that central inhibition of dopa-decarboxylase abolished the hypotensive effect of alpha-methyldopa,^{142,146} whereas previous inhibition of peripheral dopa-decarboxylase had not abolished this response. This observation seemed to suggest that methylnoradrenaline could be the active hypotensive substance, though other decarboxylated products, such as methyldopamine, could also be responsible. A further study seems to ascribe a more important role to alpha-methylnoradrenaline.¹⁴⁹ Also, methylnoradrenaline administered directly into the third and fourth ventricles of the cat had greater depressor activity than either of its precursors, methyldopa or methyldopamine.¹⁵⁰

The contribution of a central mechanism of action to methyldopa's hypotensive effects has not been defined. It has been postulated that there are central alpha-adrenergic receptors which, when stimulated by endogenous adrenergic substances or drugs, activate inhibitory neurons so that peripheral sympathetic activity is diminished. It

has been suggested that these receptors may lie in the medullary portion of the lower brain stem in the area of the nucleus tractus solitarii.¹⁵¹ A study demonstrating that pretreatment with intraventricular phentolamine, an alpha-receptor antagonist,¹⁵¹ completely prevented the hypotensive effect of systemically administered methyldopa¹⁵² seems to provide some evidence for this central theory.

This central mechanism of action has been applied to other drugs, namely clonidine.

5.4 Clonidine

The mechanism of the prolonged hypotensive action of clonidine is not fully understood. The bulk of evidence suggests a central action in the medulla, probably by alpha-receptor stimulation which decreases sympathetic activity.^{151,153-157} The evidence for the site of action of clonidine being within the central nervous system is based upon experiments showing the production of typical hypotensive and bradycardic effects by injections of minute amounts of clonidine into cerebral ventricles, obliterative neurological animal studies and the demonstration of decreased spontaneous activity in presynaptic sympathetic nerves with preservation of circulatory reflexes. Tolazoline and other alpha-adrenergic blocking agents will block the hypotensive response to clonidine.¹⁵⁸

Finally, the last group of agents, which influence the activity of the sympathetic nervous system to be discussed

are the beta-adrenergic receptor blocking drugs. Though alpha-adrenergic receptor blocking drugs, namely phentolamine and phenoxybenzamine, also alter sympathetic activity, they will not be discussed. These agents have not been useful for the therapy of most patients with essential hypertension, although they do appear to decrease the arterial pressure in some patients with "high renin" essential hypertension.¹⁵⁹

On the other hand, beta-adrenergic receptor blocking drugs are very effective agents in the treatment of essential hypertension.

5.5 Beta-adrenergic receptor blocking drugs

It has proved very difficult to demonstrate convincingly the antihypertensive effect of beta-receptor antagonists in animals, although there is no doubt as to their effectiveness in the management of hypertension in man.¹⁶⁰ The difficulties encountered in obtaining an antihypertensive effect with beta-receptor antagonists have been largely responsible for the fact that their mode of action still remains obscure. The mechanisms which may be involved are numerous and no single mechanism can be claimed to be wholly responsible.

Beta-receptor blocking drugs vary considerably in their pharmacological characteristics. Many decrease both the rate and the force with which the heart contracts. These actions lead to a reduction in cardiac output which could result in a reduction in blood pressure through adaptive changes.^{161,162} It has also been suggested that blockade of

cardiac beta-receptors might reduce sympathetically-mediated pressor reflexes and that the baroreceptors would gradually become 'reset' to regulate blood pressure at a lower level.^{I63} This hypothesis, too, is probably untenable. Transient rises in blood pressure evoked by a variety of stimuli still occur under beta-receptor blockade both in man and in animals.^{I64-I70}

Beta-receptor blocking agents have also been shown to inhibit the release of noradrenaline from nerve endings in a manner very similar to that of guanethidine.^{I68-I70} This effect can be detected at concentrations considerably lower than those necessary to block uptake. Inhibition of both uptake and release are shared equally by both enantiomers and have been attributed to membrane-stabilizing activity.^{I71-I73} Neither effect can be considered, therefore, to contribute to the antihypertensive activity of these agents.

An additional explanation for the adrenergic neurone blocking action of beta-receptor antagonists have been suggested. In experiments in guinea-pig isolated atria,^{I74} the overflow of tritiated noradrenaline evoked by nerve stimulation is increased by isoprenaline and decreased by propranolol. This inhibitory effect of propranolol was obtained at a concentration which had no effect on neuronal uptake of noradrenaline. The authors of these experiments proposed the following hypothesis. Noradrenaline release by nerve stimulation can be modulated by two different pre-junctional mechanisms. Low concentrations of noradrenaline in the synaptic gap would activate pre-junctional beta-receptors,

leading to an increase in the amount of noradrenaline released per stimulus. High concentrations of noradrenaline would activate pre-junctional alpha-receptors, leading to an inhibition of transmitter release. Pre-junctional beta-receptors are also present in sympathetic neurones innervating blood vessels.¹⁷⁵ It is conceivable that blockade of these receptors could reduce transmitter release and consequently, vasomotor tone.

A central effect has also been implicated as a mechanism for the hypotensive effect of beta-receptor antagonists. Administration of beta-receptor antagonists into the cerebral ventricles induces prolonged hypotension and bradycardia.¹⁷⁶⁻¹⁸⁰ The reduction in blood pressure and heart rate are probably the result of blockade of central beta-receptors in that the dextro-enantiomers of propranolol and alprenolol, which are devoid of beta-receptor blocking activity, have no depressant effect on either blood pressure or heart rate. Also, it has been reported that, in the conscious rabbit, blood pressure falls following intra-cerebroventricular administration of propranolol are paralleled by a reduction in pre-ganglionic sympathetic nerve activity.¹⁸¹ Although it seems that beta-receptor antagonists can influence central sympathetic activity, there are considerations that mitigate against this being the explanation for their antihypertensive action in man. First, beta-receptor antagonists that fail to penetrate into the central nervous system, such as practolol¹⁸²

and sotalol,¹⁸³ are effective antihypertensive drugs in man. Secondly, the effects described by most investigators in animals are of acute onset, unlike the response seen in man.¹⁶³

It is possible that drugs with such wide actions as a beta-receptor antagonist may act to lower the blood pressure by more than one mechanism.

For all these agents, the mechanism of hypotensive effect cannot be explained by inhibition of sympathetic activity alone. Since the renin-angiotensin system also seems to contribute to the regulation of blood pressure, any influence on this system may contribute to the overall blood pressure lowering effect of these drugs. Reserpine,¹⁸⁴ methyldopa,¹⁸⁵ clonidine,^{157,186} and beta-adrenergic blocking agents¹⁸⁷ lower renin and aldosterone. However, the renal secretion of renin is not suppressed and actually may be increased with guanethidine therapy.¹⁸⁸ The conflicting effect of these drugs on renin seems to suggest that inhibition or stimulation of renin-release alone does not explain the hypotensive effect of these drugs.

Whatever their mechanism, their hypotensive effect results in either decreased peripheral resistance or decreased cardiac output or both.

As all of these drugs are effective in lowering blood pressure, the selection of a drug from this group will often depend on incidence of related side effects.

Severe depression is one of the most serious side

effects associated with reserpine therapy. It has also been suggested that the use of reserpine may be associated with the development of breast cancer. Although not confirmed by subsequent analyses, such an association is difficult to disprove definitely. Consequently, the use of reserpine has diminished with the availability of newer and safer antihypertensive drugs.

The undesirable effects of guanethidine are quantitative extensions of the therapeutic effects and are due to excessive sympathetic blockade or unopposed parasympathetic activity. Orthostatic hypotension, delayed or retrograde ejaculation and severe diarrhea have been frequently associated with guanethidine therapy. The clinical use of guanethidine has been largely reserved for severely hypertensive individuals unresponsive to other regimens.

Common side effects related to methyldopa therapy include drowsiness, fatigue, dry mouth, and diarrhea. Methyldopa also possesses side effects unrelated to its other pharmacologic actions. Rarely, it can cause drug fever and hemolytic anemia. Compared to reserpine and guanethidine, methyldopa has a lower incidence of side effects. It is often preferred by many clinicians to clonidine. The side effects of clonidine are generally not serious but many are annoying. Dry mouth, sedation, drowsiness and constipation are common. Occasionally, a withdrawal syndrome has been reported following the sudden

cessation of therapy. This has largely discouraged its use because of the concern of lack of compliance.

The beta-adrenergic blocking drugs, such as propranolol, are probably preferred to many of these drugs as side effects associated with their use are less annoying to the patient. However, serious adverse effects can occur in patients with borderline congestive heart failure, bradyarrhythmias, asthma and chronic bronchitis.

It would seem that, for many hypertensive patients, methyldopa may be the preferred antihypertensive agent in light of its efficacy and side effects. It is frequently used as adjunctive therapy with diuretics and vasodilators. The mechanism of action of these agents will be briefly reviewed only.

5.6 Diuretics

The precise mechanism of action of oral diuretics as antihypertensive agents is unknown. The antihypertensive effect of these agents has been attributed to plasma volume and extracellular fluid contraction,¹⁸⁹⁻¹⁹¹ sodium imbalance,¹⁹² decreased receptor sensitivity to vasopressor substances^{193,194} such as angiotensin, and direct arteriolar vasodilation.^{191,192}

The extent of diuresis necessary to produce the maximal antihypertensive action of thiazides does not necessarily have to be great. Small doses of a thiazide, for example 25 mg hydrochlorthiazide, will produce little change in serum electrolytes but have about as much anti-

hypertensive action as much larger doses.¹⁹⁵⁻¹⁹⁷

The diuretics can potentiate the hypotensive action of the other antihypertensive drugs in patients who do not respond adequately to a diuretic alone. During treatment, sodium and water retention can occur and counteract the effects of the sympatholytic drugs; the arterial pressure then becomes a direct function of the plasma volume. The diuretics are effective in preventing sodium retention and thereby increase the efficacy of the sympatholytics.¹⁹⁸

5.7 Vasodilators

Hydralazine is considered the prototype of this group of drugs. Although prazosin was initially introduced as a vasodilator agent, further studies revealed that this was probably not its mechanism of action. However, it will be briefly described in this section.

The direct and indirect effects of hydralazine are almost entirely limited to the cardiovascular system. The drug may diminish total peripheral vascular resistance by 60 per cent or more.^{199,200} Early investigators attributed the peripheral hypotension to a centrally mediated inhibition of sympathetic discharge.²⁰¹⁻²⁰⁴ Several papers have again credited hydralazine with a very limited central vaso-depressor action.²⁰⁵

However, the predominant inducer of systemic hypotension is the direct relaxation of smooth muscle in the peripheral vascular bed.^{200,206-208} The relaxation in

in vascular resistance vessels is much greater than that in capacitance vessels.^{199,200,206,208} Systolic blood pressure falls less than diastolic blood pressure; pulmonary artery pressure may be slightly increased.²⁰⁰

Hydralazine-induced peripheral hypotension may be counteracted and reduced by as much as 75 per cent by the combined activity of three mechanisms.^{199,209} Foremost is an increase in heart rate and contractibility and therefore, an increase in cardiac output.^{199,200,206,210,211} The actions are primarily reflex in nature, although a central stimulatory component has been identified.^{201,212,213} Second, an increase in plasma renin has been demonstrated during vasodilator therapy.^{214,215} Propranolol has been shown to effectively block both of these mechanisms.²¹⁶ Third, tolerance to hydralazine's hypotensive action develops with sodium and water retention unless diuretics are added to the therapy.^{199,214,217,218}

Although prazosin was introduced as a vasodilator, the exact mechanism of its action is unknown. Prazosin has direct smooth-muscle relaxant effect demonstrated in animals, but chiefly a post-synaptic alpha-receptor blocking activity in man.²¹⁹ Unlike other vasodilators, there is no reflex tachycardia and no renin elevation.²²⁰

6. CLINICAL THERAPY OF ESSENTIAL HYPERTENSION

The term, hypertension, has been defined, based on criteria set by the World Health Organization,²²¹ as:

"...a blood pressure of 160 mm Hg systolic and 95 mm Hg diastolic and above. A normal range consists of a blood pressure below 140 mm Hg systolic and 90 mm Hg diastolic. The intermediate group, 140 mm Hg systolic, 90 mm Hg diastolic to 159 mm Hg systolic, 94 mm Hg diastolic, has been referred to as 'borderline or possible' hypertension."

These criteria are practical for screening large populations with only a single casual blood pressure but have no inherent value in reaching a decision on who should be treated.

For therapeutic reasons, hypertension becomes that level of blood pressure at or above which evaluation and treatment do more good than harm. Based on the results of the Veterans' Administration trials,^{II-I3} all patients with a diastolic blood pressure of 105 mm Hg or greater should be treated with antihypertensive drug therapy. The goal of therapy in these patients should be to achieve and maintain diastolic pressure levels at less than 90 mm Hg with minimal adverse effects.

Treatment of patients with diastolic pressures from 90 to 104 mm Hg should be individualized. In these patients with "borderline" hypertension, risk factors that influence the decision to begin drug treatment include elevated systolic pressure, presence of target organ damage, family history of the complications of hypertension, male sex, smoking habits, elevated blood cholesterol levels, and diabetes.²²² The goal of therapy in "borderline" hypertension whether it consists of dietary measures or pharmacological intervention, is also to achieve and maintain diastolic

pressure levels at less than 90 mm Hg, or as closely to this as possible, with minimal adverse effects.

The U.S. Joint Committee on Detection, Evaluation and Treatment of High Blood Pressure has recommended a stepped-care approach to treatment.²²³ This therapeutic approach has recently been recommended, with certain modifications, by a Canadian task force.²²⁴ Stepped-care refers to the plan of therapy in which mild antihypertensive agents are initially prescribed in low doses and subsequently increased; more potent drugs are added, one after the other, if needed, until some predetermined goal of blood pressure is reached.

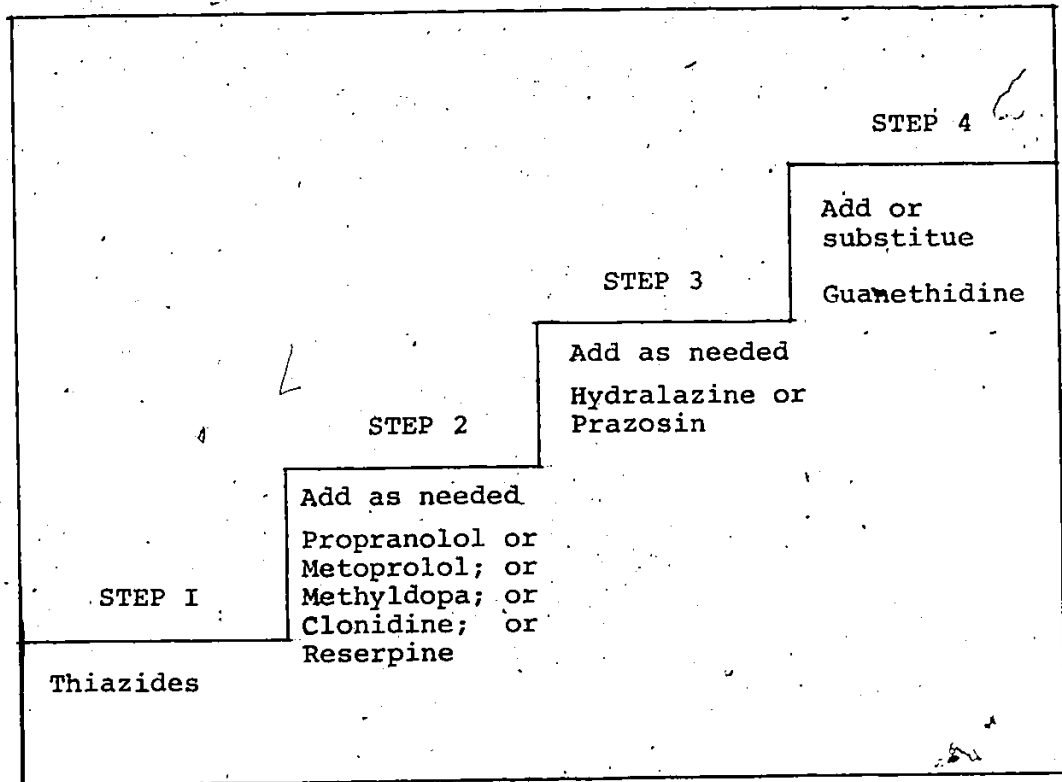
The proposed stepped-care plan, as suggested by Kuchel et al²²⁴ and the U.S. Joint Committee²²³ is schematically illustrated in figure I. While there are many possible effective therapeutic regimens, the regimens outlined in figure I were chosen "because experience suggests that they produce the desired control of high blood pressure with a minimum of side effects and patient inconvenience."²²³

7. THE PROBLEM OF COMPLIANCE

These guidelines for treatment of essential hypertension have promoted an improved and standardized management of hypertension. However, despite such effective regimens, many hypertensive patients suffer or die each year of the complications of hypertension. The reason for this is at least two-fold. Firstly, a large percentage of the hypertensive population remains undiagnosed and therefore untreated. In a community screening project in Edmonton,

FIGURE I

Stepped-care antihypertensive drug therapy



up to 37 per cent of hypertensive Canadians were unaware that they had high blood pressure.²²⁵ However, in interpreting these data, two points must be recognized:

(a) many Canadians with high blood pressure readings at this screening program may and, most probably, will have normotensive readings on subsequent examination and therefore their unawareness is appropriate; (b) some clinicians may be perfectly aware of their patients' elevated blood pressure but have elected, for any series of reasons, not to tell them. Therefore, the rate of awareness obtained in this survey may be spuriously high. Nevertheless, unawareness remains a significant problem and effective screening programs are continuously being sought. Secondly, some hypertensive patients are aware of their blood pressure levels and, though effective regimens are being prescribed for them, their blood pressure is not effectively controlled. The main problem in this case is poor patient compliance. In order to achieve systematic blood pressure reduction, patients must take 80 per cent or more of their drugs before they will exhibit systematic decline in blood pressure.²²⁶ Low compliance is responsible for one third²²⁷ to three-fourths²²⁸ of the failures to achieve goal blood pressure in hypertensive patients.

Caldwell and others followed-up 76 hypertensive patients who had been started on antihypertensive drugs at a Detroit hospital and found that half had dropped out

of care by eleven months. Only 17 per cent of these patients were still under care for their hypertension five years later.²²⁹ Two other studies found that it may be difficult to keep hypertensive patients under care long enough even to begin therapy. Finnerty and others found that only 50 per cent of hypertensives discovered during a Washington, DC population survey kept a follow-up clinic appointment.²³⁰ Fletcher and others discovered that only 58 per cent of hypertensives found in a Baltimore Emergency Room kept their subsequent appointments at the hospital's clinic.²³¹

More recent drop-out data have come from special hypertension care programmes and are considerably more optimistic. Only 7 per cent of a group of Hamilton steel workers dropped-out of care in the first six months of therapy.²³² and only 3 per cent of New York department store employees dropped-out in the first year of care.²³³ Furthermore, 20 per cent of Chicago employees dropped-out of the first year of an antihypertensive care programme, although an additional 3 per cent were lost the next year.²³⁴ Finally, of 224 new and old hypertensive patients in a Hamilton general practice, 11 per cent dropped-out or moved away within the next year.²³⁵

A number of compliance improving strategies have been suggested; these suggestions range from patient education programmes through negotiated treatment "contracts" to calendar packs of medications. All of these recommendations are plausible and some are feasible but almost none has

undergone any experimental evaluation in randomized trials to see whether it works.

In the possibility that a better understanding of compliance as a phenomenon would provide ideas for compliance improving strategies, much effort has gone to identifying the determinants of compliance. Medication compliance diminishes markedly with the passage of time, and most antihypertensive regimens must be life-long. It has been suggested that compliance is lower when regimens are complex²³⁶⁻²³⁷ and some hypertensives require several tablets per dose and multiple doses per day in order to achieve or approach goal blood pressure. Most hypertensives are symptom free at the time that treatment is started, another feature which apparently discourages compliance. Furthermore, symptomless hypertensives who feel worse on treatment than they did before treatment began must overcome a considerable urge to quit taking their medications.

As mentioned previously, several compliance-improving strategies have been suggested. By far, one of the simpler means of improving compliance would be to simplify the drug regimen. It has been suggested that compliance may be improved by minimizing the number of drugs a patient must take or by minimizing the number of doses to be taken.²³⁶⁻²³⁹

Recent studies in the clinical literature raise questions regarding the widely accepted belief that in order

for an antihypertensive drug to be effective, it must be administered several times a day. Several studies now lend support to single or twice daily dosing with certain drugs.

Several current studies have shown propranolol to be effective in lowering blood pressure when administered on a twice-a-day^{240-1,303} or even once-a-day schedule.²⁴²⁻²⁴⁴ This prolonged effect seems to suggest that the therapeutic half-life does not necessarily correlate directly with the biologic half-life of propranolol, which is approximately six hours.²⁴⁵ This disparity may be due to the longer half-life of active metabolites or to saturation of the tissue with active drug which maintains effectiveness after blood concentrations have declined.²⁴⁰

Clonidine has also been studied in a once daily dosing schedule.²⁴⁶ With the once daily dose, blood fluctuations were much wider than they were during three-times-a-day therapy, with the greatest blood pressure readings occurring near the end of the dosing interval. Most patients preferred the once-a-day dosage regimen because of the lack of drowsiness during the day. Since mild to moderate drowsiness is a major disadvantage of clonidine therapy, this once-a-day approach may improve compliance.

Studies have shown that when used with a diuretic, hydralazine is effective and safe when administered to hypertensive patients in a twice daily dosage schedule.²⁴⁷⁻²⁵⁰

The data from a large multicentre study of 194 patients suggested a significant number of patients receiving hydralazine four-times-a-day may be treated with comparable efficacy on a twice-a-day dosage regimen. The only major difference appeared to be a slightly greater incidence of dizziness or lightheadedness on the twice-a-day schedule.²⁴⁷ The mechanism for this long action of hydralazine is not known, since the half-life has been reported to be between 1.5 and 8 hours, depending on the acetylation rate.^{251,252} Studies in rodents have shown that hydralazine is rapidly taken up and retained by the arterial vessels and then released slowly, thus producing a longer duration of action.²⁴⁹

Prazosin has also been effective in several studies when administered on a twice-a-day schedule, rather than the recommended three-times-a-day schedule.^{253,254}

However, there is little work to suggest simplifying a methyldopa regimen. As it is recommended by the manufacturer, methyldopa is usually administered in three or four divided doses. At the time this study was designed, only one study of single daily dosing of methyldopa had been described in the literature.²⁵⁵ However, in this study, the total dose was given in the morning and many of the patients complained of day-time drowsiness. The hypothesis of the present study, then, was to determine if single daily dosing of methyldopa could maintain blood pressure control throughout the day and also minimize the side effect of drowsiness by administering this total dose at bedtime. In a recent

double-blind cross-over study,²⁵⁶ the antihypertensive effectiveness of methyldopa was shown to be similar in 14 patients, whether the drug was administered three times a day or as a single dose. This study, as well as the one by Jain and others²⁵⁵ suggest that the therapeutic half-life of methyldopa is longer than the observed plasma half-life.

Since methyldopa is an effective antihypertensive drug and is, in fact, one of the more widely prescribed, any attempt to improve compliance with this agent seems warranted.

8. PHARMACOKINETICS OF METHYLDOPA

A review of the literature of the pharmacokinetic parameters of methyldopa was undertaken in an attempt to determine the possibility of single daily dosing with this drug. The information available, though scanty, is summarized under the headings of absorption, distribution, metabolism and excretion.

8.1 Absorption

Methyldopa is incompletely absorbed from the gastrointestinal tract after oral administration. It has been reported that 50 per cent^{257,258} to as little as 9 to 18 per cent^{139,259-261} of an oral dose is absorbed. Such variation may partially explain the range of doses necessary for adequate blood pressure control. In addition, the bioavailability of unaltered methyldopa may be less than the total amount of drug absorbed. Stenbaek and co-workers showed that 11 per cent of an oral dose was absorbed as the acid-labile con-

jugate²⁶² probably formed by intestinal wall metabolism.²⁶³

In these studies, a different methodology was used for the assay of methyldopa and this may explain the discrepancy of the results. Although absorption following oral administration has been reported to vary considerably, the average serum level of unconjugated methyldopa, in one study, corresponded "fairly well" with the oral dose given.²⁶⁴

8.2 Distribution

In rats, intravenous methyldopa is widely distributed in various tissues, particularly in the kidneys.²⁶⁵

In man, the apparent volume of distribution has been calculated to be 0.29 ± 0.08 litres per kilogram.²⁶⁰ This volume of distribution does not correspond with any identifiable physiologic space. Since it is less than total body water and more than extracellular fluid volume, this value for volume of distribution has been suggested to imply a "rapid transfer of methyldopa from plasma to tissues with high rates of blood flow."²⁶⁰ Methyldopa does not bind significantly to plasma proteins.^{257,266,267} No therapeutic blood concentration range has been determined for methyldopa. Peak serum concentrations are reported to occur between 2 and 6 hours following an oral dose.^{139,257,260} Following a single 500 mg oral dose, peak serum concentrations of 0.95 and 2.8 ug/mL occurred in 2 to 3 hours.²⁶⁰ After the intravenous administration of 200 mg, peak concentrations of 8 to 10 ug/mL were reported.²⁶⁶ In seven patients with essential hypertension, receiving an average dose of methyldopa of 1.3 g

per day, average serum concentrations, determined 4 hours after the morning dose, were 2.93 ug/mL.²⁶⁴ In patients with renal disease and azotemia, receiving an average oral dose of 27I mg/day, the average serum concentration of methyldopa, determined four hours after the morning dose, amounted to 0.7I ug/mL.²⁶⁴ However, when plasma methyldopa levels and blood pressure control were compared, no significant relationship was found.^{139,260} This lack of correlation between plasma levels of methyldopa and antihypertensive effect may support the suggestion that the antihypertensive efficacy of methyldopa is determined by a metabolite of methyldopa at a specific site in the central nervous system.¹⁴⁸

After a single oral dose, in four patients, the antihypertensive effects of methyldopa began in 4 to 5 hours, and some effect was still noticeable after 24 hours.²⁶⁸ After 2.0 to 2.5 grams of intravenous methyldopa, in twelve patients, maximum blood pressure lowering response occurred 10 to 20 hours after the administration of the drug.²⁶⁹ This delay in the maximum response to intravenously administered methyldopa may also support the suggestion that the antihypertensive efficacy of methyldopa is determined by a metabolite of methyldopa.

8.3 Metabolism

Methyldopa is partially metabolized in man but the extent of this metabolism and the nature of the metabolic products seems to be dependent upon the route of administration.

After a single oral dose, significant amounts of acid labile conjugates, mainly the methyldopa-O-sulphate,^{257,260,270} appear in the plasma and after long-term oral administration 60 per cent of chemically determined methyldopa in plasma and urine is in these conjugated forms.²⁶³ In contrast, intravenous methyldopa results in negligible amounts of these conjugates possibly suggesting that this metabolic transformation takes place in the intestinal wall and that under these conditions enterohepatic circulation of methyldopa is minimal. However, significant enterohepatic circulation and reabsorption has been proposed to explain the relatively greater amount which is conjugated after repeated oral doses.²⁷¹

The exact position of the sulfate group on the molecule has not been determined, but it has been suggested that the 3-oxygen position would be the most susceptible under physiologic conditions.²⁵⁷ Methyldopa mono-O-sulfate possesses the same antihypertensive properties as methyldopa when administered parenterally or by injection to hypertensive rats.²⁷² Its antihypertensive effect has not been assessed in man.

Methyldopa undergoes decarboxylation and beta-hydroxylation in brains of mice and rabbits,¹³⁸ but in man, probably no more than 5 to 10 per cent of a given dose of methyldopa is decarboxylated.^{139,257}

8.4 Elimination

After a single 500 mg oral dose, 12 to 17 per

cent of the drug is excreted unchanged in the urine.¹³⁹

Up to 74 to 96 per cent of the drug is excreted unchanged after an intravenous dose of methyldopa. Methyldopa is excreted in the urine mainly as metabolites, the sulfate conjugate accounting for 64 per cent of the urinary metabolites.²⁵⁷ Other metabolites that have been identified include α -methyldopamine, 3-O-methyl-methyldopamine, and 3,4-dihydroxyphenylacetone.²⁵⁸

The plasma half-life is reported to be 1.67 hours in patients with normal renal function and 3.57 hours in patients with advanced renal failure.²⁶⁶

The overall elimination constant has been determined to be $0.56 \pm 0.03/\text{hour}$ and based on an apparent volume of distribution of 20.2 ± 1.5 litres, the clearance rate has been calculated to be 11.2 ± 0.6 litres/hour.²⁶⁰ This rate is almost twice the normal creatinine clearance (6.3 to 9.0 litres/hour)²⁷³ and could suggest that methyldopa elimination is dependent on factors other than glomerular filtration, that is, it may depend on metabolic pathways^{274,275} in addition to renal excretion of unmetabolized drug, or on renal tubular secretion.

In patients with impaired renal function, it has been suggested that there is increased conjugation of methyldopa by the liver for its elimination.²⁶⁴ However, the percentage of methyldopa excreted as the sulfate conjugate does not always correlate with renal failure.²⁵⁷ No correlation between the amount of sulfate conjugate excreted

and antihypertensive effect has been found.

8.5 Conclusion

The only information from this review of the pharmacokinetic parameters of methyldopa which encourages the investigation of single daily dosing is the finding that the antihypertensive effect of methyldopa has been reported to last up to 24 hours. This suggests that the therapeutic half-life may be much more prolonged than the reported biological plasma half-life of 1.67 hours.

9. SUMMARY AND BASIS HYPOTHESIS

Many studies^{267,277} have suggested that compliance might be improved by minimizing the number of drugs a patient must take or by minimizing the number of doses to be taken. In 1973, Jain and co-workers²⁵⁵ did a study to investigate the feasibility and efficacy of a single morning dose of methyldopa. Their results showed that there was no significant change during the day in the average control mean arterial pressure. Their findings in fact suggested a more prolonged effect from single doses of methyldopa.

Another factor which influences compliance is the incidence and acceptance of side effects induced by drug therapy. Many hypertensive patients are asymptomatic when they are diagnosed. Many of the drugs they must take will create symptoms, often unpleasant, thus discouraging compliance. One of the most common side effects with methyldopa is drowsiness and lethargy. In the study by Jain and co-workers, excessive drowsiness from single morning doses was

noted.²⁵⁵ Giving the total dose at night might minimize the drowsiness experienced and might even have a beneficial sedative effect for the patient.

It has been shown that methyldopa can be given as a total dose without loss of blood pressure control. Possibly it could be given as a total bedtime dose without loss of blood pressure control and with minimization of side effects such as drowsiness and lethargy. This study was undertaken to investigate this possibility.

CHAPTER II

EXPERIMENTAL DESIGN

This chapter presents the procedures involved in conducting an experiment to compare (1) the effectiveness of two dosage regimens of methyldopa to control and/or maintain baseline blood pressure, and (2) the incidence of side effects with these two regimens.

I. PATIENT SAMPLE

Patients were eligible to the study if they met definite criteria. Patients, diagnosed previously as hypertensives and receiving methyldopa as part of their therapy for at least one month, were admissible to the study. In particular, patients receiving methyldopa in a three times a day schedule were sought. It was understood that, since methyldopa causes salt retention, patients on methyldopa therapy would also be receiving a diuretic. However, patients receiving other antihypertensive drugs, in addition to methyldopa and a diuretic, were not admissible to the study. Finally, all patients receiving this specific regimen of methyldopa and a diuretic, were considered for admission to the study only if their blood pressure was considered, by their physician, as controlled or sufficiently maintained at a stable level.

Patients were excluded from the study if they were

taking antihypertensive agents other than methyldopa and a diuretic, and if they were taking sedatives or hypnotics which could interfere with the evaluation of side effects, namely drowsiness and lethargy. Patients, whose dosage of methyldopa or diuretic had to be continuously adjusted, were also excluded from the study. Patients with renal or liver impairment were not admissible to the study.

The physician's consent to the patient's participation in the trial was obtained verbally. The patient was then requested to sign a consent form (Appendix A).

The total number of patients expected to complete the study was twenty (20).

2. STUDY DESIGN

The study was designed as a double-blind study, and also a crossover trial. Following a two-week observation period, considered the baseline, patients were randomly assigned to one of two treatment schedules adjusted to provide equal numbers of patients in each treatment schedule. The randomization was assigned by the manufacturer, Merck, Sharp and Dohme Laboratories, who supplied the investigator with methyldopa placebo and active tablets. Each schedule consisted of two four-week blocks, illustrated in figure 2. The total daily dose administered to each patient during the trial was equivalent to that previously required to control or maintain the blood pressure at a stable level.

FIGURE 2

Treatment schedulesTreatmentRegimen

A

4 weeks methyldopa qH.S.^a
followed by
4 weeks methyldopa T.I.D.^b

B

4 weeks methyldopa T.I.D.
followed by
4 weeks methyldopa qH.S.

a H.S.: at bedtime

b T.I.D.: three times a day

No alterations of drug dosage were allowed throughout the trial. It was decided that if a patient's blood pressure became uncontrollable during the trial, the patient would be discontinued from the study and medications administered as considered necessary by the treating physician.

To ensure the double blindness of the study, methyldopa placebos were utilized. During the two four-week crossover periods, the medication was supplied for the patient. Patients were instructed to take one tablet three times a day from bottle A and three tablets at bedtime from bottle B. Depending on the assigned treatment schedule, bottle A and bottle B contained either placebo or active tablets of methyldopa. The investigator was blinded as to the contents of these bottles.

3. MEASUREMENTS

Patients participating in the study attended clinics at the Family Medicine Centres of the Ottawa General Hospital and the Ottawa Civic Hospital. Prior to the commencement of the study, a medical history was done or obtained from the chart if the patient had recently been seen by the physician. A medication history was done on all patients by the investigator (Appendix B).

Patients were assessed weekly. They were required to visit the clinic once a week, in the morning, on the same day each week. In the evening of each clinic visit, the investigator visited the patients' homes for further blood pressure measurements.

3.1 Blood pressure measurements

At each clinic visit, blood pressure measurements were taken in the sitting, standing and supine positions with a five minute interval between positions. Three readings were taken in each position at two minute intervals. The same measurements were repeated in the evening. These readings were recorded on a weekly flowsheet (Appendix C).

A discussion of blood pressure measuring technique is warranted at this time. Two methodologies of blood pressure measurement are available to an investigator: direct and indirect. The direct methods are highly-developed, of known and precise accuracy, yield large quantities of data, but are seldom used in clinical investigations mainly because of their essentially invasive nature. The most commonly used techniques involve placing a cannula in an artery and attaching a pressure-sensitive device to the external end. The signal from the transducer can be led directly to amplifiers and an on-line recorder to produce an immediate record of blood pressure and wave form. The equipment required for direct measurements has restricted measurements to the laboratory. The indirect methods are poorly developed, of dubious accuracy and yield only small quantities of data. However, almost all published studies of the effects of drugs on blood pressure have been performed using an indirect method of measurement. In the experiment herein described, an indirect method of measurement was therefore used.

All indirect methods are firmly based upon the occluding cuff technique devised by workers such as Hill and Barnard,²⁷⁸ Riva-Rocci,²⁷⁹ and Korotkoff,²⁸⁰ and which has altered very little since their time.

In summary, a cuff containing an inflatable rubber bag is wrapped around the arm. The bag is then inflated by means of a one-way hand pump until the radial arterial pulse disappears. A valve on the pump is then partially released and the pressure within the bag allowed to fall. The bag is connected to a mercury-in-glass manometer which expresses the pressure in terms of millimeters of mercury (mm Hg). The pressure corresponding to the first appearance of a pulse in the brachial artery below the cuff is taken as a measure of the systolic pressure.

Korotkoff detected reappearance of a pulse in the collapsed brachial artery as a succession of sounds accompanying each heart beat and appreciated by means of a stethoscope applied to the artery below the cuff. He defined different kinds of sound appearing as the pressure fell from phase I (initial sound - sharp and of high frequency) to phase IV (disappearance of high frequency leaving only low frequency noise - "muffling") and phase V (cessation of noise). Many investigations have been conducted into the genesis of Korotkoff sounds and these were summarized by Burton²⁸¹ as follows: "The walls of the artery below the inflated cuff fall together to form a flat ribbon. As the cuff pressure falls, a systolic pulse will

eventually succeed in penetrating the length of the cuff and temporarily distend the artery below. The transverse section of the artery will expand to an ovoid and flow will be highly turbulent, vibrating the tissues around and then collapsing again. Many comparisons of direct and indirect measurements agree that the first Korotkoff sound is a sensitive indicator of systolic pressure. As the pressure continues to fall, each successive pulse which penetrates the cuffs adds to the volume of blood in the system below until a point is reached at which the collapsed segment remains distended between beats but flow remains turbulent. In theory, the critical opening pressure of the artery has been exceeded in diastole and this must equal the diastolic pressure. The failure to collapse between beats should lead to a loss of high frequency components with the next systolic expansion - thus there is a clear theoretical link between diastolic pressure and phase IV. As the cuff pressure continues to fall, a point is reached at which the artery remains fully distended, flow becomes laminar, and the succeeding systolic pulse produces no significant vibration of surrounding tissues; the Korotkoff sounds disappear."

There has been considerable controversy over the years about which of these two points should be taken as diastolic pressure - phase IV or phase V - and even official recommendations have been known to differ.²⁸² Physiological studies comparing direct and indirect pressures have also

differed in their conclusions.^{283,284} Whatever the results of scientific studies, it is felt that the difference between phase IV and phase V is usually so small as to be of little consequence in the light of the known inaccuracies of the whole technique. It is theoretically correct to take phase IV as approximating diastolic pressure.²⁸⁵ One of the reasons for this decision is that phase IV is less variable than phase V following exercise and in certain diseased states when an increased cardiac output is present, such as in aortic regurgitation, severe anemia and thyrotoxicosis. In these conditions and in some individuals, presumably with a hyperkinetic circulation, there may be no fifth phase or disappearance of sound, that is Korotkoff sounds can be heard all the way down to zero on the sphygmomanometer. Nevertheless, it is felt that phase V (the disappearance of sound) is usually closer to the true diastolic pressure than is the beginning of phase IV.²⁸⁶ It is the experience of many investigators that there is far greater reproducibility in recording phase V within and between observers than with phase IV. Since phase V depends on the presence or absence of sound, its determination is dependent only on the hearing acuity of the examiner, on the level of room noise, and on technique. The problem is further compounded by the fact that some persons lack a phase IV. Lastly, the great majority of physicians have traditionally considered diastolic pressure as the disappearance of sound. For these reasons, phase V is con-

sidered by most the correct criterion for diastolic pressure. In this experiment, the diastolic pressure was determined by phase V.

There are many factors which may add to the inaccuracy of an indirect reading. It is now well-established that the bag must be applied snugly over the artery; for adults the cuff must be at least 12 cm wide and, for the best results, should be 20 per cent wider than the diameter of the arm²⁸⁵ with similar and carefully detailed recommendations for children of all ages. Obese patients with arms of greater than 20 cm diameter present a problem. There appears to be increasing over-reading of pressure with increasing arm diameter beyond this size and correcting tables are available.²⁸⁷

The rate of cuff deflation is also important and, if not accurately standardized, can produce marked discrepancies in repeated observations.

The reliability of the instrument used for blood pressure recording also contributes to the accuracy of the blood pressure reading. Mercury-in-glass manometers are reliable and easily maintained and, provided the system is cleaned and degreased once every six months, there is little that can go wrong. Anaeroid manometers must be calibrated against a mercury-in-glass manometer at six months intervals. In this experiment, an anaeroid sphygmomanometer was used mainly because of the convenience of portability.

The greatest single problem in blood pressure recording is the competence of the observer in measuring blood pressure accurately. In specific tests, graduate nurses demonstrated standard deviations of up to 16 mm Hg systolic and 45 mm Hg diastolic in rereading the same prerecorded and filmed blood pressures.²³⁸ Physicians performed no more reliably.²³⁹ The following sources of observer error and variability are now well recognized:²³⁹

- (a) hearing loss: the Korotkoff sounds are low-energy acoustic phenomena, often just above the normal hearing threshold when monitored with a stethoscope. Thus environmental noises may cause difficulties. Auditory acuity is therefore required of any blood pressure observer;
- (b) observer bias: there is often unconscious observer bias toward over- and under-reading a blood pressure;
- (c) terminal digit preference: strong preferences for certain terminal digits - particularly "0" and "5" - has been consistently demonstrated;
- (d) mental concentration and reaction time;
- (e) rates of inflation and deflation and proper placement of the cuff.

In an attempt to reduce the inter-observer variability, in this experiment, the same observer took blood pressure measurements at all times. It was assumed that the sources of error with one observer would be less than with several observers.

3.2 Recording of side effects

During the clinic visit, patients were assessed regarding side effects of the therapy using a questionnaire (see Appendix D). The questionnaire was conducted in an informal manner. While waiting between blood pressure measurements, the questions regarding side effects were asked, generally following the order in which they appeared on the questionnaire. The frequency of symptoms for each treatment schedule were then assessed and compared.

3.3 Compliance

Compliance with the regimen was estimated from a weekly tablet count. Patients were not informed of this but were simply asked to bring in their medication, so that an adequate supply of medication could be supplied for the following week.

A compliance factor was estimated for each patient. This factor was defined as a value corresponding to the ratio of the number of tablets missed to the total number of tablets to be taken. This value was then multiplied by 100 to give a percentage of compliance. Therefore, a compliance factor of 100 per cent represented "perfect" compliance.

Patients were also required to fill in a compliance calendar on which they recorded the times at which they took each dose of methyldopa (Appendix E).

3.4 Plasma methyldopa determinations

Patients were also requested to provide a blood

sample for analysis of plasma methyldopa levels. Laboratory technicians, at the Family Medicine Centres of the Ottawa General and Ottawa Civic hospitals, accepted to take the blood samples. They recorded sampling time on the sample tube.

Blood samples were taken weekly for determination of plasma methyldopa levels. The methodology used for the assay was that described by Myhre et al²⁶⁶ and is herein described. In principle, methyldopa and methyldopamine are oxidized to highly fluorescent trihydroxyindole derivatives. The assay was performed by mixing 1.0 mL of serum with 2.0 mL of distilled water and 0.5 mL of cold 1N perchloric acid. The test tube was placed in icewater for 30 minutes and centrifuged. Exactly 2.0 mL of the supernatant was transferred to a 10 mL graduated test tube and neutralized with potassium carbonate (10 per cent) using methylred as indicator (pH approximately 6). Then, 1.0 mL of a phosphate buffer and 4.0 mL of distilled water were added, and the sample was oxidized by addition of 200 μ L of 0.25 per cent (W/V) of potassium ferricyanide. The tube was shaken and kept at room temperature for exactly 5 minutes. Then, 1.0 mL of a freshly prepared mixture of 9 parts 5N sodium hydroxide and 2 parts 2 per cent ascorbic acid (W/V) were added. The tube was shaken and left at room temperature for 105 minutes. The tube was shaken now and then (5 times). The fluorescence emitted at 500 nm was read in a spectrophotometer (Aminco Bowman) during activation of the sample

at 400 nm. All values were corrected for any non-specific fluorescence by the plasma blank.

Plasma methyldopa levels were estimated from the curve of optical density versus concentration, drawn up using standard known concentrations of methyldopa (Appendix F). The plasma methyldopa determinations reflect both unconjugated and conjugated methyldopa and methyldopamine.

Possible interference in methyldopa estimation by other drugs was examined by Barnett et al.²⁶⁰ No interference was demonstrated with allopurinol, amiloride, bethanidine, chlorothiazide, clonidine, cyclopenthiiazide, debrisoquine, digoxin, guanethidine, hydralazine, prindolol and propranolol. Only dipyridamole showed interfering fluorescence.

Several studies have shown that there is no correlation between plasma levels of methyldopa and its antihypertensive effect.^{139,263,274} However, a correlation between the blood pressure lowering action and the amount of the 3-O-methylated metabolites has been suggested.²⁷⁴

3.5 Determination of plasma renin activity

After each four-week treatment schedule, an additional blood sample was taken for determination of plasma renin activity. Methyldopa therapy usually lowers plasma renin activity.¹⁸⁵ As the patients were admitted to the study only if maintained for at least one month on methyldopa, no baseline value for plasma renin activity could be determined. The plasma renin activity was determined

only in an attempt to assess any influence of the treatment schedules.

The radioimmunoassay, which as done by the biochemistry laboratory of the Ottawa General Hospital, is based on the method described by Sealy et al.²⁸⁸

4. STATISTICAL ANALYSIS

The data were subjected to an analysis of variance for crossover designs.^{289,290} Blood pressure control or maintenance was defined as being a difference from control values of less than 10 mm Hg for the mean arterial pressures throughout the study. The null hypothesis, that there was no difference in blood pressure control or maintenance between the total evening dose regimen and the multiple dose regimen, was rejected at the 0.05 level.

CHAPTER III

RESULTS

This chapter presents the results of the experiment comparing (1) the effectiveness of two dosage regimens of methyldopa to control and/or maintain baseline blood pressure, and (2) the incidence of side effects with these two regimens.

I. PATIENT SAMPLE

Despite an intermittent study period of three years, at the University of Ottawa affiliated Family Medicine Centres of the Ottawa General and Ottawa Civic Hospitals, the patient sample only numbered 10. More than 1,000 charts were reviewed manually and using the computer system at the Family Medicine Centre of the Ottawa Civic Hospital. Of these, 105 charts revealed patients receiving methyldopa therapy three times a day. Fifty charts were from the Ottawa General Hospital and 55 were from the Ottawa Civic Hospital. Only 10 of these patients (9.5 per cent) participated in the study. Physicians refused approval for 43 (40.9 per cent) patients because of the patient's age, medical condition or psychological disposition. In certain cases, it can be assumed that the physician preferred not to jeopardize the patient-physician relationship. By far the greatest loss of candidates was due to patients' refusal to participate in such a study. Fifty-

two (49.6 per cent) patients did not want to participate because of the 10-week duration of the study, inconvenience of coming to the clinic weekly, blood sampling, interference with working schedule, unwillingness to alter present therapy despite physician's approval, and lastly because of unsuccessful attempts to contact these candidates.

Patients #2 and #7 withdrew from the study due to complaints of side effects allegedly associated with the therapy. The remaining eight patients (#1, #3, #4, #5, #6, #8, #9, #10) were therefore included in the study analysis. Of these, four patients received the multiple dose (T.I.D.) regimen, followed by the total evening dose (H.S.) regimen (Treatment A) and four patients received the H.S. regimen followed by the T.I.D. regimen (Treatment B).

The demographic data for this patient population is presented in Table 1. All patients had required methyldopa for maintenance of blood pressure at a controlled or stable level. None of the patients had secondary hypertension. The duration of their hypertensive disease ranged from 4 to 15 years. Seven of the eight patients were being treated with methyldopa 250 mg three times a day; one patient was treated with 500 mg three times a day. All patients had received this regimen of methyldopa for at least one month prior to the study. The total dose of methyldopa administered to each patient during the trial was equivalent to that previously required to control and/or maintain the blood pressure at a stable level. All patients were also receiving diuretic therapy.

2. ANALYSIS OF BLOOD PRESSURE MEASUREMENTS

Blood pressure measurements, for each position and time, as specified in the protocol, are represented in tables 2A through 2F. For purpose of analysis, the systolic and diastolic pressures were

combined and represented as the mean arterial pressure. The mean arterial pressure is a value equivalent to the diastolic pressure plus one-third the pulse pressure. The pulse pressure is calculated as the difference between the systolic and diastolic pressure. The control mean arterial pressures were similar in both treatment groups, for each position and for each measurement time, as outlined in tables 3A, 3B, 3C.

The differences between the mean arterial pressures of the control period and each treatment period were submitted to a crossover analysis of variance, for each position separately. The sources of variation considered were the patients themselves, the sequence of administration of the treatment schedule, the treatment regimen itself, the time of blood pressure measurement and a combination of the regimen as affected by time. All other sources of variation that could not be identified were considered in the residual component. These analyses are represented in tables 4A, 4B and 4C.

In the sitting position, there was a statistically significant difference in the mean arterial pressures between the two regimens of drug administration ($p < 0.05$) and this difference was in favor of the single bedtime dosing regimen in that, mean arterial pressures during this regimen were even lower than the baseline values. There was also a statistically significant difference in the morning and evening mean arterial pressures within each drug regimen ($p < 0.01$), with mean arterial pressures significantly lower in the morning. When looked at separately, mean arterial pressures were lower in the evening on the multiple dose regimen and lower in the morning on the total evening dose regimen. It is possible that the difference in the mean arterial pressures between the two regimens of drug administration may have been associated with the difference in morning and evening mean arterial pressures which normally occur.

However, on further analysis of the standing position, there was also a statistically significant difference between the two regimens ($p < 0.05$), in favor of the total evening dose regimen, but there was no significant difference between the two regimens with regard to time of blood pressure measurement ($p > 0.05$).

In the supine position, there was also a statistically significant difference between the regimens ($p < 0.01$) but the significance of the difference was solely attributed to the difference in morning and evening mean arterial pressures.

In all positions, the sequence of the crossover trial had no significant effect on the blood pressure.

The null hypothesis was rejected as there was a significant difference between the multiple dose regimen and the total evening dose regimen ($p < 0.05$). This difference was in favor of the total evening dose regimen in that the average mean arterial pressure attained was significantly lower than the baseline values.

These differences in mean arterial pressures were further analyzed in terms of systolic and diastolic blood pressures recorded in order to assess which component of the blood pressure was more significantly affected (Table 5).

In the sitting position, there was a statistically significant difference in the systolic blood pressure between each drug regimen ($p < 0.025$), in favor of the total evening dose regimen. Analysis of the diastolic blood

pressure indicated that the combined effect of the regimen and time of blood pressure measurement was a significant source of variation ($p < 0.05$). The contribution of the regimen alone could therefore not be determined. The data and analysis are represented in tables 6A, 6B, 6C and 6D.

In the standing position, there was a statistically significant difference also in the systolic blood pressure between the two drug regimens ($p < 0.025$), in favor of the total evening dose regimen. Analysis of the diastolic pressure indicated also that the combined effect of treatment regimen and time of measurement was a significant source of variation ($p < 0.01$), with the time of measurement contributing significantly to this variation ($p < 0.025$). The data and analysis are represented in tables 6E, 6F, 6G and 6H.

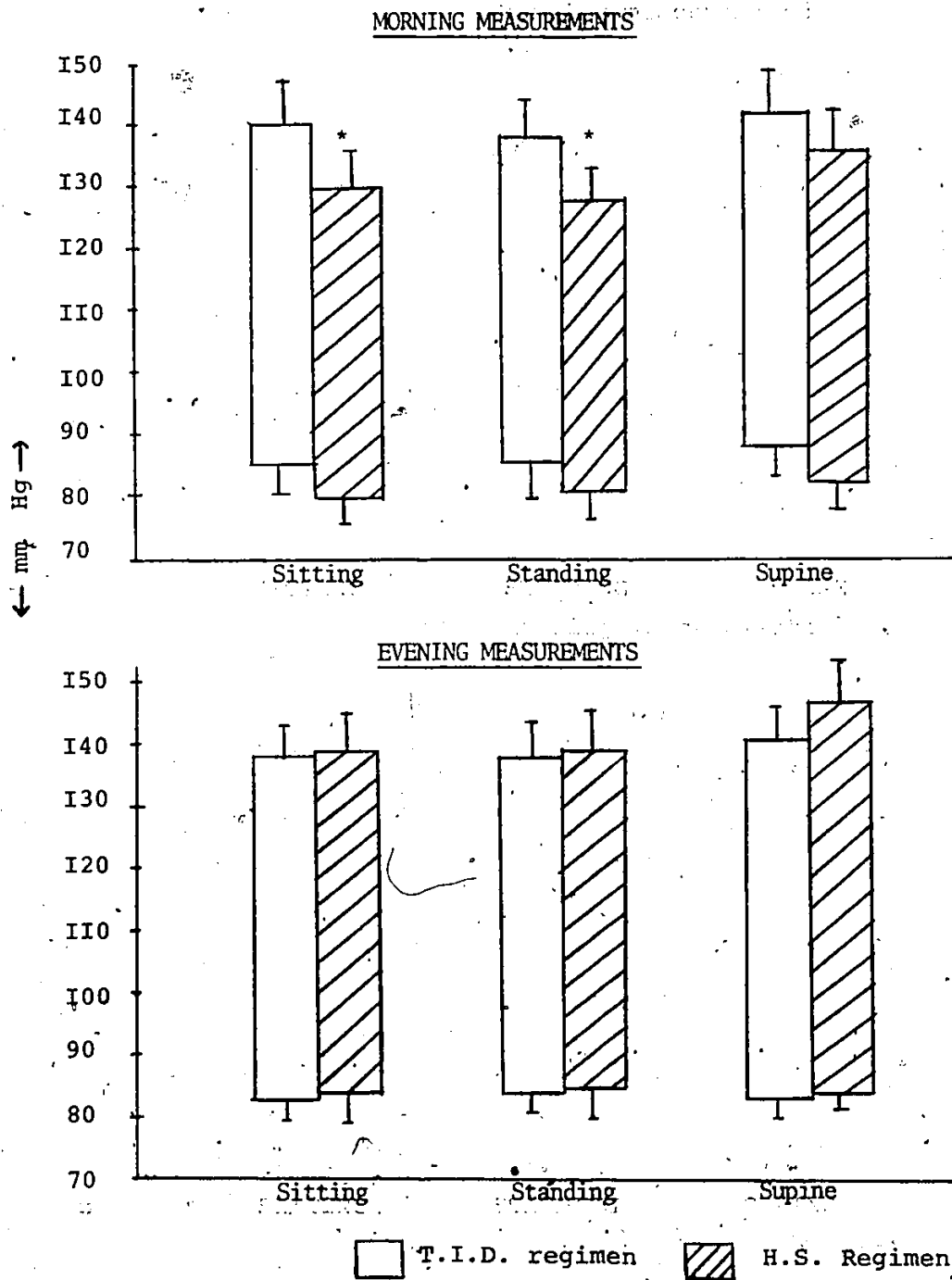
In the supine position, there was no significant difference ($p > 0.05$) in either the systolic or diastolic blood pressure between the two drug regimens. The data and analysis are represented in tables 6I, 6J, 6K and 6L.

In summary, there was a significant difference in the mean arterial pressures between the multiple dose regimen and the total evening dose regimen. The difference was in favor of the total evening dose regimen. The enhanced lowering of blood pressure with the total evening dose regimen is accounted for by a greater decrease in the systolic blood pressure.

A schematic representation of these results is presented in figure 3.

FIGURE 3

Schematic representation of
systolic and diastolic blood
pressure



*Significantly different at the $p < 0.025$ level

3. SIDE EFFECTS

By far, the most frequent side effects noted throughout the study were drowsiness and dry mouth. Urinary frequency, dizziness, headache and diarrhea were sometimes reported. Affirmative and negative answers to the questionnaire were recorded weekly. An estimation of the incidence of side effects for each regimen is presented in Table 7. There was no significant difference in incidence of side effects associated with each regimen. Table 8 lists the complaints volunteered by the patients and indicates the therapy they were taking at that time.

Patients #2 and #7 withdrew from the study because of side effects allegedly attributed to the therapy. Both of these patients reported the side effects after initiation of the single dosing regimen. Patient #2 complained of cramps in the legs and of feeling very sleepy on awakening in the morning. These side effects were so worrisome to the patient that further participation in the study was not volunteered. Patient #7 described a pounding sensation in the head within a couple of days of initiation of the crossover trial and particularly in the early afternoon. As this patient also suffered from emphysema, this side effect may have been associated to the medical condition. However, the patient was convinced that he was taking the single dose regimen and felt that the regimen was not suited for someone who also had breathing difficulties. Further participation in the study was not volunteered.

When the blood pressure results of these drop-outs are examined, there does not appear to be any difference between the control blood pressure measurements and the single dose blood pressure measurements, though the paucity of data does not allow an analysis. The blood pressure measurements are summarized in table 9.

It is difficult to assess whether the side effects experienced by the drop-out patients were associated with the drug regimen though it cannot be ruled out.

As outlined in table 8, several patients experienced some trouble with their sleeping patterns with both regimens but more frequently with the single bedtime dose regimen. This may be related to administration of a single large dose.

4. COMPLIANCE

As described in the experimental design, compliance was estimated from a pill count and a compliance factor was assigned to each patient. The compliance factor assigned to each patient in the study are summarized in table 10. The mean compliance factor was 98.8 ± 1.0 per cent.

When questioned about compliance, patient #3 admitted to missing three tablets. Once the code was broken, it was determined that these tablets corresponded to three placebo tablets. Patient #8 admitted to missing three tablets also but, in this case, it corresponded to three active tablets. Patient #9 also admitted to missing one dose only, and it corresponded to an active methyldopa tablet. The other patients always indicated that they had

taken all the medications prescribed. An equal number of placebo and active tablets were missed throughout the trial, as outlined in table II. The omission of doses therefore probably did not contribute to the difference in mean arterial pressures seen with the two drug regimens.

5. PLASMA METHYLDOPA LEVELS

Only five patients (#3, #4, #5, #8, #10) agreed to give weekly blood samples for a measurement of plasma methyldopa. Patient #1 refused to participate in the study if blood samples were required. Patients #6 and #9 did not come to the clinic for weekly visits but were assessed at their home and office respectively. Facilities for blood sampling were not available for these patients.

The time interval between administration of dose and blood sampling varied depending on the scheduled time of visit of the patient to the clinic. For all patients, plasma methyldopa levels were determined at some time following the morning dose. The time interval between the morning dose of methyldopa and the actual time of blood sampling was recorded weekly. The time interval for the two-week control period was 115.5 ± 39.8 minutes. The time interval for the two four-week trial periods was 127.4 ± 38.0 for the single dose regimen and 118.5 ± 41.3 minutes for the multiple dose regimen. These data are outlined in table I2.

The estimated plasma methyldopa levels are presented in table I3. The average control plasma methyldopa level was 0.79 ± 0.29 mcg/mL. The average plasma methyldopa level

during the single dosing regimen was 0.56 ± 0.18 mcg/mL, and the average plasma methyldopa level during multiple dosing was 0.62 ± 0.24 mcg/mL. From this data, it is difficult to determine whether the dosing schedule affected the plasma methyldopa level as the values for both regimens are similar and the standard error of the mean is quite large.

6. PLASMA RENIN ACTIVITY (PRA)

Blood samples were drawn at week 6 and week 10 for determination of plasma renin activity. Since patients participating in the study were maintained on methyldopa for several months, no attempt was made to obtain a pre-therapy plasma renin activity and no attempt was made to classify the patients as hypo-, hyper-, or normoreninemic patients.

The mean plasma renin activity for three patients on the H.S. regimen was 1.2 ± 0.2 ng/mL/hr and for four patients on the T.I.D. regimen, it was 1.4 ± 0.5 ng/mL/hr. Though the number of measurements does not permit a statistical comparison, there does not seem to be a difference between the two regimens. Both values would be considered normoreninemic.

This data is summarized in table I4.

TABLE I: DEMOGRAPHIC DATA

<u>PATIENT NUMBER</u>	<u>SEX</u>	<u>AGE</u>	<u>ANTIHYPERTENSIVE DRUGS*</u>	<u>OTHER DRUGS</u>
#1	F	58	Aldomet 250 mg tid Dyazide i daily	Diabeta 10 mg daily
#3	M	59	Aldomet 250 mg tid HCTZ 50 mg daily	
#4	F	57	Aldomet 250 mg tid Naturetin K 5 mg qam	Bellergal spacetabs i qam PRN
#5	F	55	Aldomet 250 mg tid Dyazide i qam	Deladumone inj. q2-3mths Beclovent i puff qid Ventolin inhaler PRN Entrophen 300 mg tid Maalox i tbsp qid
#6	F	67	Aldomet 250 mg tid HCTZ 100 mg daily	Coumadin 5 mg daily Slow-K 600 mg ii qid Isordil 5 mg SL PRN Digoxin 0.25 mg daily Nitroglycerin 0.6 mg SL PRN
#8	F	63	Novodopamet 250 mg tid HCTZ 100 mg daily	Insulin
#9	F	47	Aldomet 500 mg tid HCTZ 50 mg daily	
#10	F	59	Aldomet 250 mg tid Hygroton 50 mg qam	

* Tradenames listed

TABLE 2A: BLOOD PRESSURE - SITTING (AM)

Triplicate blood pressure recordings
measured in the sitting position
in the morning

Pt no →	#1	#2	#3	#4	#5	#6	#7	#8	#9	#10
Week ↓										
Wk 1	I44/90 I54/92 I42/90	I28/80 I26/76 I26/78	I60/96 I56/92 I40/92	I32/82 I32/82 I40/82	I60/I00 I58/98 I60/98	I30/62 I40/70 I38/66	I42/72 I42/74 I40/72	I44/80 I46/78 I42/78	I20/82 I28/90 I24/88	I52/90 I48/98 I52/84
Wk 2	I40/80 I44/84 I32/84	I28/80 I28/82 I30/82	I52/I00 I52/I00 I60/I02	I30/76 I26/80 I28/80	I62/I02 I62/I00 I56/I04	I32/70 I36/74 I34/70	I42/70 I44/68 I38/60	I42/82 I38/82 I44/84	I28/82 I26/80 I22/80	I34/82 I38/86 I34/84
Wk 3	I40/80 I38/76 I38/78	I18/80 I26/80 I24/80	I78/I10 I66/I00 I78/I08	I30/76 I30/76 I28/72	I56/98 I48/88 I54/I00	I38/78 I36/76 I38/72	I38/68 I38/70 I40/68	I32/78 I36/88 I34/86	I24/80 I24/82 I22/80	I30/78 I30/78 I28/82
Wk 4	I44/90 I42/90 I44/90	DC	I52/98 I52/96 I58/96	I10/78 I12/70 I18/72	I52/I02 I38/96 I36/96	I26/66 I30/64 I24/64	DC	*	I12/80 I14/80 I16/80	I18/72 I20/76 I20/74
Wk 5	I38/90 I44/90 I32/84		I64/I02 I66/I02 I62/I02	I28/80 I30/78 I28/78	I58/96 I54/92 I58/96	I24/68 I28/72 I22/68		I30/66 I28/72 I28/74	I18/80 I22/80 I26/84	I28/74 I28/78 I28/76
Wk 6	*		I70/92 I70/94 I68/94	I22/72 I24/78 I26/76	*	I28/68 I30/70 I30/66		I22/74 I24/76 I24/78	I28/82 I24/80 I22/80	*
Wk 7	I60/I00 I54/92 I40/92		*	I22/80 I26/84 I22/80	I28/84 I34/84 I44/90	I20/68 I20/66 I20/68		I22/78 I22/76 I18/80	I12/80 I18/80 I22/84	I42/82 I40/82 I44/82
Wk 8	I50/98 I50/96 I48/92		I52/96 I62/I02 I54/I02	I36/80 I42/84 I44/84	I22/84 I24/84 I26/84	I10/58 I10/54 I14/56		I22/80 I22/78 I24/76	I32/82 I22/82 I22/82	I42/78 I36/76 I42/76
Wk 9	*		I52/98 I52/96 I48/96	I30/82 I40/80 I38/82	I38/86 I40/88 I38/86	I20/60 I18/60 I18/58		I24/72 I22/74 I22/72	I20/78 I22/80 I20/78	I32/86 I30/86 I30/88
Wk 10	*		*	I44/68 I46/82 I46/82	I50/90 I38/I00 I62/I00	*		I10/64 I16/64 I14/62	*	I38/80 I28/76 I28/78

* Patient not available at that time

DC Dropped out of study

TABLE 2B: BLOOD PRESSURE - SITTING (PM)

Triplicate blood pressure recordings
measured in the sitting position
in the evening

Pt no → Week ↓	#1	#2	#3	#4	#5	#6	#7	#8	#9	#10
Wk 1	I46/80 I48/80 I42/78	I26/80 I32/82 I22/80	I52/96 I70/I00 I60/I00	I32/82 I36/82 I54/80	I60/90 I70/90 I68/94	I52/64 I34/72 I36/74	I28/64 I50/64 I40/62	I44/70 I30/70 I34/72	I28/80 I26/82 I28/84	I40/84 I40/88 I44/90
Wk 2	I42/86 I48/90 I50/92	I20/80 I22/80 I26/82	I60/I04 I60/I04 I60/I04	I40/86 I40/88 I36/78	I54/92 I42/88 I42/88	I34/70 I30/70 I42/72	I42/72 I44/70 I46/68	I38/90 I36/78 I38/82	I24/84 I22/90 I22/86	* * *
Wk 3	I50/84 I58/90 I56/86	I26/76 I28/80 I22/76	I60/I02 I60/I02 I60/I02	I42/88 I40/88 I38/86	I50/98 I50/92 I50/92	I32/68 I28/62 I30/66	I48/72 I48/70 I50/72	I22/72 I20/70 I18/70	I26/80 I28/80 I26/82	I32/88 I34/98/ I38/I00
Wk 4	I56/86 I50/84 I32/84	DC	I64/90 I62/92 I60/92	I30/90 I38/80 I30/78	I50/98 I52/98 I50/96	I32/62 I30/62 I34/62	DC	* * *	I20/88 I20/78 I18/82	I28/80 I30/80 I30/80
Wk 5	I38/74 I40/84 I42/84		I60/98 I60/98 I60/I02	I38/80 I40/80 I36/80	* * *	I28/64 I30/66 I28/64		I28/76 I30/80 I30/82	* * *	I36/88 I38/88 I38/88
Wk 6	* * *		I68/I02 I66/96 I62/I02	I22/72 I24/74 I26/76	I60/92 I58/92 I62/94	* * *		I30/82 I26/80 I28/80	I28/80 I28/82 I26/82	I38/80 I34/80 I34/82
Wk 7	I60/90 I50/88 I40/82		I76/92 I76/98 I70/I08	I36/82 I22/78 I22/80	* * *	I28/62 I24/68 I28/64		I26/72 I26/74 I24/76	I30/88 I22/82 I22/82	I32/90 I30/88 I32/88
Wk 8	I32/78 I32/78 I34/76		I58/I02 I56/I02 I58/98	I34/82 I34/80 I30/82	I60/90 I48/92 I40/88	I20/60 I22/60 I28/64		I28/68 I24/70 I20/68	I32/82 I24/84 I24/82	I34/82 I38/82 I36/82
Wk 9	I42/86 I52/88 I58/88		I62/I04 I62/I06 I66/I06	I28/78 I30/80 I26/78	I70/I02 I70/I02 I68/I00	I28/64 I22/62 I22/62		I22/78 I22/72 I20/72	I20/80 I22/80 I22/82	I32/82 I32/84 I36/86
Wk 10	* * *		I70/I06 I70/I06 I64/I04	I38/78 I32/78 I34/76	I62/98 I58/98 I58/98	* * *		I22/80 I20/82 I22/82	I20/78 I22/78 I18/78	I28/80 I28/80 I26/82

* Patient not available at that time

DC Dropped out of study

TABLE 2C: BLOOD PRESSURE - STANDING (AM)

Triplicate blood pressure recordings
measured in the standing position
in the morning

Pt no → Week↓	#1	#2	#3	#4	#5	#6	#7	#8	#9	#10
Wk 1	I54/80 I44/88 I48/90	I40/90 I40/92 I32/90	I50/98 I50/I00 I50/I00	I38/84 I34/80 I32/80	I58/98 I58/98 I56/96	I42/78 I40/76 I38/76	I38/64 I28/64 I32/64	I42/80 I40/82 I42/80	I22/72 I18/80 I18/82	I38/84 I42/84 I40/82
Wk 2	I56/92 I56/90 I54/88	I48/88 I32/82 I34/84	I60/I02 I52/I02 I52/I02	I30/80 I32/80 I42/82	I56/94 I52/96 I50/98	I26/70 I30/72 I38/74	I22/58 I30/66 I30/68	I32/82 I34/82 I32/80	I18/80 I22/88 I22/88	I34/84 I28/78 I32/80
Wk 3	I38/82 I38/80 I38/82	I38/88 I38/84 I28/80	I74/I08 I72/I08 I76/I08	I24/74 I28/74 I26/74	I60/I00 I56/98 I50/90	I28/68 I38/74 I38/70	I40/60 I40/62 I30/70	I32/80 I34/88 I32/88	I26/80 I22/80 I24/80	I28/80 I26/80 I26/80
Wk 4	I38/88 I44/92 I40/90	DC	I62/I00 I72/96 I64/I02	I20/70 I20/78 I08/78	I44/96 I40/92 I42/92	I30/70 I30/72 I34/74	DC	* * *	II4/82 II4/76 II4/78	I04/74 II2/80 II4/76
Wk 5	I34/82 I38/86 I38/84		I60/I00 I58/I00 I64/I00	I18/76 I18/72 I22/76	I58/I04 I58/I02 I58/I04	I30/70 I30/68 I30/74		I20/70 I20/72 I32/76	II4/80 II8/82 II6/86	I18/72 II2/70 I08/70
Wk 6	* * *		I72/I02 I68/I04 I72/I04	I28/78 I24/76 I26/80	* * *	I26/66 I20/66 I20/66		I24/78 I28/78 I24/78	II8/80 II8/82 I20/80	* * *
Wk 7	I58/98 I40/90 I42/92		* * *	I26/78 I22/78 I26/80	I22/78 I26/84 I20/80	I24/68 I24/66 I22/68		II8/74 II4/72 II6/72	II8/82 II8/82 I22/80	I28/80 I36/82 I36/80
Wk 8	I48/92 I50/98 I48/92		I52/I08 I54/I10 I68/I10	I42/84 I36/84 I36/84	I28/80 I24/84 I24/88	I04/56 II0/58 II8/60		I22/76 I26/78 I26/76	II8/82 I20/82 I20/84	I28/78 I32/80 I34/80
Wk 9	* * *		I54/I04 I54/I00 I58/I06	I36/82 I30/78 I32/80	I34/96 I50/96 I50/98	II8/64 II8/66 II8/62		I20/68 I24/70 I22/74	II8/78 I20/84 I22/84	I30/84 I28/86 I28/88
Wk 10	* * *		* * *	I44/80 I42/82 I42/82	I58/98 I52/96 I50/98	* * *		II0/62 I08/64 I08/62	* * *	I22/78 I22/78 I22/76

* Patient not available at that time

DC Dropped out of study

TABLE 2D: BLOOD PRESSURE - STANDING (PM)

Triplicate blood pressure recordings
measured in the standing position
in the evening

Pt. no → Week ↓	#1	#2	#3	#4	#5	#6	#7	#8	#9	#10
Wk 1	*	I18/80	I60/I00	I40/82	I66/90	I42/72	I28/64	I34/72	I32/82	I34/84
	*	I22/82	I60/98	I48/76	I62/90	I38/66	I32/64	I34/72	I28/82	I34/82
	*	I24/80	I50/98	I38/80	I60/90	I40/70	I30/62	I44/74	I26/86	I40/82
Wk 2	I52/82	I32/80	I60/I04	I32/78	I58/98	I40/70	I10/60	I46/90	I28/82	*
	I48/90	I26/82	I58/I04	I42/78	I56/96	I36/76	I42/72	I36/90	I28/88	*
	I50/90	I32/84	I60/I04	I42/82	I54/98	I42/72	I42/70	I38/90	I30/90	*
Wk 3	I60/90	I30/78	I60/I08	I32/80	I52/94	I32/68	I28/68	I20/74	I30/82	I38/78
	I80/98	I28/80	I70/I10	I40/80	I36/92	I36/70	I34/70	I22/78	I28/80	I42/82
	I58/90	I30/80	I62/I08	I40/78	I44/96	I34/70	I26/70	I24/78	I30/80	I38/88
Wk 4	I44/84		I52/I00	I28/82	I54/92	I40/76		*	I22/80	I22/78
	I42/82	DC	I60/98	I28/78	I44/86	I44/72	DC	*	I18/82	I30/76
	I42/82		I62/I02	I54/80	I52/98	I44/70		*	I20/84	I28/82
Wk 5	I46/86		I60/98	I38/80	*	I30/66		I24/72	*	I32/82
	I44/88		I66/98	I40/78	*	I30/66		I24/78	*	I28/82
	I46/88		I52/98	I40/78	*	I32/68		I22/78	*	I34/82
Wk 6	*		I72/96	I22/76	I32/88	*		I28/82	I18/82	I36/82
	*		I68/96	I30/78	I50/94	*		I28/78	I18/80	I36/78
	*		I60/96	I22/78	I54/88	*		I24/76	I20/84	I42/80
Wk 7	I56/88		I80/I08	I20/78	*	I34/68		I22/80	I22/82	I38/88
	I58/I00		I78/I06	I28/80	*	I30/66		I28/80	I22/80	I38/84
	I58/90		I66/I08	I28/78	*	I30/68		I24/82	I22/82	I38/80
Wk 8	I38/80		I64/I02	I20/76	I50/90	I26/64		I08/62	I24/84	I34/88
	I50/82		I64/I04	I20/76	I48/92	I22/62		I18/70	I24/82	I34/80
	I34/80		I68/I08	I28/78	I58/I04	I24/64		I20/70	I24/82	I28/78
Wk 9	I60/92		I64/I10	I26/74	*	I26/64		I24/70	I24/88	I32/78
	I56/90		I62/I08	I28/70	*	I22/62		I24/74	I24/86	I32/82
	I60/94		I64/I08	I28/78	*	I24/64		I26/78	I24/84	I34/84
Wk 10	*		I78/I04	I30/76	I58/I02	*		I18/78	I18/82	I30/74
	*		I72/I02	I30/76	I60/I00	*		I22/82	I22/82	I32/82
	*		I70/I06	I28/76	I58/98	*		I22/82	I20/82	I30/82

* Patient not available at that time

DC Dropped out of study

TABLE 2E: BLOOD PRESSURE - SUPINE (AM)

Triplicate blood pressure recordings
measured in the supine position
in the morning

Pt. no Week↓	#1	#2	#3	#4	#5	#6	#7	#8	#9	#10
Wk 1	I58/I04	I32/82	I70/I00	I38/86	I58/98	I38/68	I42/78	I50/90	*	I42/90
	I56/I02	I30/82	I70/I10	I38/84	I58/I00	I34/64	I52/82	I48/86	*	I38/90
	I56/I00	I34/84	I60/I02	I42/88	I58/98	I34/64	I50/80	I48/88	*	I44/88
Wk 2	I58/I02	I32/78	I60/I10	I42/84	I64/I04	I32/68	I44/70	I40/82	I34/84	I42/88
	I56/I00	I28/78	I62/I08	I44/90	I60/I02	I34/72	I42/68	I38/82	I34/90	I48/84
	I56/I00	I32/80	I70/I10	I44/84	I58/I04	I36/68	I40/74	I38/88	I22/88	I40/84
Wk 3	I32/82	I34/82	I72/I08	I28/74	I58/I00	I32/72	I50/66	I42/92	I22/80	I32/72
	I34/84	I28/82	I72/I08	I32/78	I58/98	I34/72	I48/82	I40/90	I20/80	I34/78
	I32/80	I32/82	I78/I10	I30/78	I54/98	I30/72	I48/80	I36/90	I24/82	I24/78
Wk 4	I38/86		I64/I02	I34/80	I48/92	I32/72		*	I14/78	I26/82
	I36/86	DC	I66/I04	I28/78	I42/90	I30/72	DC	*	I14/78	I20/76
	I36/86		I68/I04	I32/78	I42/88	I34/72		*	I16/74	I26/78
Wk 5	I70/I00		I70/I08	I40/82	I58/98	I22/68		I32/76	I26/88	I30/78
	I70/I00		I78/I10	I38/82	I68/I04	I26/70		I28/76	I24/84	I30/78
	I68/98		I78/I08	I40/76	I62/96	I30/72		I26/78	I26/88	I30/78
Wk 6	*		I68/I04	I32/80	*	I26/68		I28/78	I18/88	*
	*		I66/I04	I28/72	*	I28/70		I22/76	I28/88	*
	*		I72/I04	I38/78	*	I28/68		I28/78	I26/86	*
Wk 7	I66/I10		*	I42/82	I36/82	I22/66		I20/76	I22/84	I44/88
	I50/I10		*	I38/82	I34/80	I24/66		I20/80	I22/84	I42/84
	I60/I04		*	I32/82	I40/80	I24/66		I20/80	I26/84	I42/86
Wk 8	I58/98		I78/I08	I32/86	I28/84	I12/60		I28/82	I26/86	I36/78
	I60/I00		I72/I06	I36/82	I34/84	I18/58		I24/82	I24/82	I32/80
	I54/98		I78/I08	I42/82	I34/98	I04/62		I28/86	I20/82	I34/80
Wk 9	*		I70/I08	I34/82	I40/92	I24/62		I22/68	I18/82	I30/92
	*		I66/I08	I32/84	I46/96	I22/62		I24/66	I22/80	I32/90
	*		I64/I04	I42/82	I48/88	I18/62		I22/66	I18/78	I30/88
Wk 10	*		*	I50/88	I60/94	*		I20/78	*	I24/80
	*		*	I56/88	I62/94	*		I22/84	*	I22/80
	*		*	I54/84	I58/92	*		I30/86	*	I22/78

* Patient not available at that time

DC Dropped out of study

TABLE 2F: BLOOD PRESSURE - SUPINE (PM)

— Triplicate blood pressure recordings
measured in the supine position
in the evening

Pt no → Week ↓	#1	#2	#3	#4	#5	#6	#7	#8	#9	#10
Wk 1	I40/82 I42/84 I40/80	I18/74 I26/80 I20/78	I50/98 I52/100 I50/98	I48/88 I48/88 I54/86	I62/94 I60/92 I60/88	I34/68 I28/64 I28/62	I50/74 I56/72 I54/70	I44/80 I38/80 I48/82	I34/82 I32/84 I22/86	I40/82 I40/88 I40/80
Wk 2	I48/84 I46/82 I46/82	I18/78 I22/72 I26/78	I76/102 I58/98 I64/100	I46/82 I44/84 I44/82	I62/98 I68/102 I62/100	I42/72 I32/72 I39/72	I50/72 I48/80 I48/80	I40/82 I38/82 I38/88	I40/90 I40/88 I32/88	* * *
Wk 3	I62/90 I60/88 I60/86	I18/76 I18/78 I18/76	I58/104 I62/104 I62/104	I52/82 I40/82 I40/80	I52/84 I52/80 I48/84	I38/66 I32/66 I38/70	I50/80 I50/82 I54/80	I30/82 I34/82 I28/80	* * *	I38/84 I40/90 I40/90
Wk 4	I58/92 I62/88 I60/88	DC	I54/98 I58/100 I56/98	I40/80 I42/78 I48/80	I50/90 I48/88 I50/90	I38/72 I36/70 I34/68	DC	* * *	* * *	I28/80 I30/78 I30/78
Wk 5	I58/90 I52/88 I60/94		I52/96 I52/98 I54/98	I40/82 I48/82 I42/78	* * *	I30/66 I30/64 I28/66		I30/80 I30/76 I36/78	* * *	I40/90 I38/88 I38/86
Wk 6	* * *		I58/94 I58/94 I58/92	I42/84 I42/78 I40/80	I70/102 I60/94 I62/94	* * *		I28/82 I34/82 I34/80	* * *	I38/84 I38/72 I40/82
Wk 7	I70/90 I70/90 I62/92		I74/98 I68/104 I70/100	I32/82 I28/78 I32/78	* * *	I38/70 I40/72 I36/68		I28/82 I26/82 I26/82	* * *	I38/88 I32/88 I38/84
Wk 8	I54/84 I50/78 I52/82		I68/100 I76/100 I68/102	I38/78 I24/76 I32/78	I60/82 I52/80 I54/78	I30/68 I36/70 I32/70		I24/80 I22/80 I24/80	I28/82 I24/80 I26/82	I32/72 I32/72 I30/76
Wk 9	I62/94 I60/92 I58/90		I58/98 I58/98 I60/102	I20/78 I28/78 I26/76	* * *	I30/68 I36/70 I32/70		I26/80 I28/82 I28/82	I24/84 I24/86 I24/82	I32/82 I36/78 I36/78
Wk 10	* * *		I58/98 I62/100 I70/102	I34/78 I48/80 I38/80	I70/90 I70/90 I68/82	* * *		I22/82 I22/82 I24/84	I18/78 I24/82 I22/80	I28/82 I26/82 I32/82

* Patient not available at that time

DC Dropped out of study

TABLE 3A: MEAN ARTERIAL PRESSURES - SITTING*

AM

<u>Treatment A</u>	<u>Control^a</u>	<u>First 4 weeks^b</u>	<u>Second 4 weeks^b</u>
Patient #1	105.3	103.6	113.5
#4	97.3	91.6	99.2
#9	97.3	94.2	94.2
#10	105.3	102.1	99.9
Mean	101.5	97.9	101.7
± S.E.M.	±2.1	±2.5	±3.6

Treatment B

Patient #3	115.8	121.5	116.7
#5	120.3	114.2	104.5
#6	90.8	89.3	79.5
#8	101.3	94.1	88.8
Mean	107.1	104.8	97.4
± S.E.M.	±5.9	±6.7	±7.1

PM

<u>Treatment A</u>	<u>Control^a</u>	<u>First 4 weeks^b</u>	<u>Second 4 weeks^b</u>
Patient #1	104.9	105.0	104.0
#4	101.7	98.5	96.4
#9	97.9	95.3	95.3
#10	105.3	102.1	99.9
Mean	102.5	100.2	98.9
± S.E.M.	±1.5	±1.8	±1.7

Treatment B

Patient #3	121.0	119.4	123.7
#5	112.2	114.3	117.4
#6	92.3	86.1	83.5
#8	96.9	93.2	90.7
Mean	105.6	103.3	103.8
± S.E.M.	±5.8	±7.0	±8.5

* Calculated from measured blood pressure recordings and equivalent to the diastolic blood pressure plus one-third pulse pressure (systolic minus diastolic blood pressure)

^a Calculated from average of blood pressure recordings for the 2-week period (weeks 1 and 2) prior to the crossover trial

^b Calculated from average of blood pressure recordings for the first (weeks 3-6) or second (weeks 7-10) 4-week periods of the trial

TABLE 3B: MEAN ARTERIAL PRESSURES - STANDING*

AM

<u>Treatment A</u>	<u>Control^a</u>	<u>First 4 weeks^b</u>	<u>Second 4 weeks^b</u>
Patient #1	109.3	102.9	111.7
#4	99.2	90.0	98.8
#9	94.5	93.1	94.5
#10	99.9	90.4	96.8
Mean	100.7	94.3	100.5
± S.E.M.	±2.7	±2.5	±3.3
<u>Treatment B</u>			
Patient #3	117.9	124.8	123.1
#5	116.7	115.6	105.3
#6	94.8	90.3	81.2
#8	99.7	94.9	86.4
Mean	107.2	106.4	99.0
± S.E.M.	±5.1	±7.1	±8.3

PM

<u>Treatment A</u>	<u>Control^a</u>	<u>First 4 weeks^b</u>	<u>Second 4 weeks^b</u>
Patient #1	108.2	108.8	109.7
#4	99.7	97.4	93.0
#9	99.5	95.3	96.2
#10	108.4	98.5	98.9
Mean	104.0	100.0	99.5
± S.E.M.	±2.2	±2.6	±3.1
<u>Treatment B</u>			
Patient #3	120.2	121.1	127.2
#5	115.6	110.2	116.9
#6	93.9	91.6	85.3
#8	100.5	92.7	90.9
Mean	107.6	103.9	105.1
± S.E.M.	±5.4	±6.2	±8.7

* Calculated from measured blood pressure recordings and equivalent to the diastolic blood pressure plus one-third pulse pressure (systolic minus diastolic blood pressure)

^a Calculated from average of blood pressure recordings for the 2-week period (weeks 1 and 2) prior to the crossover trial

^b Calculated from average of blood pressure recordings for the first (weeks 3-6) or second (weeks 7-10) 4-week periods of the trial

TABLE 3C: MEAN ARTERIAL PRESSURES - SUPINE*

AM

<u>Treatment A</u>	<u>Control^a</u>	<u>First 4 weeks^b</u>	<u>Second 4 weeks^b</u>
Patient #1	119.8	108.1	121.6
#4	104.4	96.4	102.7
#9	101.6	95.7	95.6
#10	105.7	94.4	100.0
Mean	107.9	98.7	105.0
± S.E.M.	±3.5	±2.8	±5.0
<u>Treatment B</u>			
Patient #3	126.2	127.9	128.4
#5	120.4	115.5	106.9
#6	89.8	90.2	81.3
#8	105.2	98.1	93.2
Mean	110.4	107.9	102.5
± S.E.M.	±7.1	±7.4	±8.8

PM

<u>Treatment A</u>	<u>Control^a</u>	<u>First 4 weeks^b</u>	<u>Second 4 weeks^b</u>
Patient #1	102.8	112.6	111.9
#4	105.8	101.3	96.1
#9	102.0	- **	95.8
#10	102.2	101.2	97.8
Mean	103.2	105.0	100.4
± S.E.M.	±0.8	±3.1	±3.3
<u>Treatment B</u>			
Patient #3	119.0	117.8	122.1
#5	117.9	111.3	109.9
#6	89.7	89.6	90.5
#8	101.9	97.3	96.0
Mean	107.1	104.0	104.6
± S.E.M.	±6.1	±5.6	±6.2

* Calculated from measured blood pressure recordings and equivalent to the diastolic blood pressure plus one-third pulse pressure (systolic minus diastolic pressure)

** Due to location limitations, no evening supine reading could be obtained for the first 4 weeks

a Calculated from average of blood pressure recordings for the 2-week period (weeks 1 and 2) prior to the crossover trial

b Calculated from average blood pressure recordings for the first (weeks 3-6) or second (weeks 7-10) 4-week periods of the trial

TABLE 4A: Difference in mean arterial pressure between treatment and control period for the sitting position

		Patient number								
Sequence		I	3	4	5	6	8	9	I0	Total
1st	AM	1.7 (H)	-5.7 (T)	5.7 (H)	6.1 (T)	1.5 (T)	7.2 (T)	3.1 (H)	13.2 (H)	32.8
	PM	-0.1 (H)	1.6 (T)	3.2 (H)	-2.1 (T)	6.2 (T)	3.7 (T)	2.2 (H)	3.2 (H)	17.9
2nd	AM	-8.2 (H)	-0.9 (H)	-1.9 (T)	15.8 (H)	11.3 (H)	12.5 (H)	3.1 (T)	6.7 (T)	38.4
	PM	0.9 (T)	-2.7 (H)	5.3 (T)	-5.2 (H)	8.8 (H)	6.2 (H)	2.2 (T)	5.4 (T)	20.9
Total		-5.7	7.7	12.3	14.6	27.8	29.6	10.6	28.5	110.0

(H) - difference from control associated with H.S. regimen
(T) - difference from control associated with T.I.D. regimen

	T.I.D.	H.S.	Total
AM	8.8	62.4	71.2
PM	23.2	15.6	38.8
Total	32.0	78.0	110.0

Analysis of variance

Source of variation	df	SS	ms	F
Patients	7	379.33	54.19	4.41
Sequence	1	2.31	2.31	0.19
Treatment (HS or TID)	1	66.13	66.13	5.38 *
Time (AM or PM)	1	111.38	111.38	9.06 **
Treatment X Time	1	117.05	117.05	9.52 **
Residual	20	245.97	12.29	1.00

* $p < 0.05$

** $p < 0.01$

TABLE 4B: Difference in mean arterial pressure between treatment and control period for the standing position

Patient number										
Sequence	I	3	4	5	6	8	9	I0	Total	
AM	6.4	-6.9	8.3	0.5	4.5	4.8	1.4	9.5	28.5	50.9
Ist	(H)	(T)	(H)	(T)	(T)	(T)	(H)	(H)		
PM	-0.6	-9.9	2.3	5.4	2.3	7.8	4.2	1.9	22.4	53.5
	(H)	(T)	(H)	(T)	(T)	(T)	(H)	(H)		
AM	-2.4	-5.2	0.4	10.8	13.6	13.3	0.0	3.1	33.6	
2nd	(T)	(H)	(T)	(H)	(H)	(H)	(T)	(T)		
PM	-1.5	-7.0	6.7	-1.3	8.6	9.6	3.3	1.5	19.9	
	(T)	(H)	(T)	(H)	(H)	(H)	(T)	(T)		
Total	1.9	-20.0	17.7	15.4	29.0	35.5	8.9	16.0	104.4	

(H) - difference from control associated with H.S. regimen
 (T) - difference from control associated with T.I.D. regimen

	T.I.D.	H.S.	Total
AM	4.0	58.1	62.1
PM	24.6	17.7	42.3
Total	28.6	75.8	104.4

Analysis of Variance

<u>Source of variation</u>	<u>df</u>	<u>ss</u>	<u>ms</u>	<u>F</u>
Patients	7	507.02	72.43	5.09
Sequence	1	0.21	0.21	0.01
Treatment (HS or TID)	1	69.62	69.62	4.89 *
Time (AM or PM)	1	12.25	12.25	0.86
Treatment X Time	1	144.97	144.97	10.19
Residual	20	284.65	14.23	1.00

* $p < 0.05$

TABLE 4C: Difference in mean arterial pressure between treatment and control period for the supine position

		Patient number								
Sequence		I	3	4	5	6	8	9	10	Total
AM		11.7 (H)	-1.7 (T)	8.0 (H)	4.9 (T)	-0.4 (T)	7.1 (T)	5.9 (H)	11.3 (H)	46.8
Ist										54.8
PM		-9.8 (H)	1.2 (T)	4.5 (H)	6.6 (T)	-0.1 (T)	4.6 (T)	- (H)	1.0 (H)	8.0
AM		-1.8 (T)	-2.2 (H)	1.7 (T)	13.5 (H)	8.5 (H)	12.0 (H)	6.8 (T)	5.7 (T)	43.4
2nd										64.6
PM		-9.1 (T)	-3.1 (H)	9.7 (T)	8.0 (H)	-0.8 (H)	5.9 (H)	6.2 (T)	4.4 (T)	21.2
Total		-9.0	-5.8	23.9	33.0	7.2	29.6	18.1	22.4	119.4

(H) - difference from control associated with H.S. regimen

(T) - difference from control associated with T.I.D. regimen

	T.I.D.	H.S.	Total
AM	21.5	68.7	90.2
PM	23.5	5.7	29.2
Total	45.0	74.4	119.4

Analysis of variance

<u>Source of variation</u>	<u>df</u>	<u>ss</u>	<u>ms</u>	<u>F</u>
Patients	7	437.55	62.50	4.39
Sequence	1	3.00	3.00	0.21
Treatment (HS or TID)	1	27.01	27.01	1.90
Time (Am or PM)	1	116.28	116.28	8.17 *
Treatment X Time	1	132.04	132.04	9.28 *
Residual	20	284.65	14.23	1.00

* $p < 0.01$

TABLE 5: SYSTOLIC AND DIASTOLIC PRESSURES

Mean systolic and diastolic pressures
for both regimens, in all positions
and for both time periods **

SITTING

Dosage regimen

AM*

PM*

T.I.D.

$$\frac{139.7 \pm 6.5}{84.9 \pm 4.6}$$

$$\frac{137.7 \pm 5.6}{82.8 \pm 3.9}$$

H.S.

$$\frac{129.7 \pm 5.5}{79.8 \pm 4.6}$$

$$\frac{139.0 \pm 6.9}{83.7 \pm 4.7}$$

STANDING

T.I.D.

$$\frac{138.4 \pm 6.8}{85.8 \pm 6.7}$$

$$\frac{137.9 \pm 6.4}{83.7 \pm 4.3}$$

H.S.

$$\frac{127.9 \pm 6.3}{80.9 \pm 5.2}$$

$$\frac{139.4 \pm 7.6}{84.7 \pm 5.0}$$

SUPINE

T.I.D.

$$\frac{142.4 \pm 7.6}{88.5 \pm 5.6}$$

$$\frac{140.6 \pm 6.3}{83.0 \pm 3.8}$$

H.S.

$$\frac{135.8 \pm 7.5}{83.0 \pm 5.2}$$

$$\frac{146.6 \pm 7.7}{84.1 \pm 3.8}$$
* Mean $\pm$ S.E.M.

** Represents the mean of the recordings obtained from 8 patients

TABLE 6A: Systolic blood pressure - sitting position

AM

<u>Treatment A</u>	<u>Control^a</u>	<u>First 4 weeks^b</u>	<u>Second 4 weeks^b</u>
Patient #1	142.7	140.0	150.3
#4	131.3	123.8	136.3
#9	124.7	121.0	121.1
#10	143.0	125.6	136.0
Mean	135.4	127.6	135.9
± S.E.M.	±3.9	±3.7	±5.2
<u>Treatment B</u>			
Patient #3	153.3	165.3	153.3
#5	159.7	150.4	137.0
#6	135.0	129.5	116.7
#8	142.7	128.7	119.8
Mean	147.7	143.5	131.7
± S.E.M.	±4.8	±7.7	±7.3

PM

<u>Treatment A</u>	<u>Control^a</u>	<u>First 4 weeks^b</u>	<u>Second 4 weeks^b</u>
Patient #1	146.0	146.9	144.4
#4	139.7	133.7	130.5
#9	125.0	124.4	123.2
#10	141.3	134.2	132.0
Mean	138.0	134.8	132.5
± S.E.M.	±3.9	±4.0	±3.8
<u>Treatment B</u>			
Patient #3	160.3	161.8	165.7
#5	156.0	153.6	159.3
#6	138.0	130.2	124.7
#8	136.7	125.8	123.0
Mean	147.8	142.9	143.2
± S.E.M.	±5.3	±7.6	±9.7

^a Average of the measured systolic blood pressures for the 2-week period (weeks 1 and 2) prior to the crossover trial

^b Average of the measured systolic blood pressures for the first (weeks 3-6) or second (weeks 7-10) 4-week periods of the trial

TABLE 6B: Difference in systolic blood pressure between treatment and control period for the sitting position

Patient number										
Sequence	I	3	4	5	6	8	9	10	Total	
AM	2.7 (H)	-12.0 (T)	7.5 (H)	9.4 (T)	5.5 (T)	14.0 (T)	3.7 (H)	17.4 (H)	48.2	80.6
Ist PM	-0.9 (H)	-1.5 (T)	6.0 (H)	2.4 (T)	7.8 (T)	10.9 (T)	0.6 (H)	7.1 (H)	32.4	
AM	-7.6 (T)	0 (H)	-5.0 (T)	22.7 (H)	18.3 (H)	22.9 (H)	3.6 (T)	7.0 (T)	61.9	102.1
2nd PM	1.6 (T)	-5.4 (H)	9.2 (T)	-3.3 (H)	13.3 (H)	13.7 (H)	1.8 (T)	9.3 (T)	40.2	
Total	-4.2	-18.9	17.7	31.2	44.9	61.5	9.7	40.8	182.7	

(H) - difference from control associated with H.S. regimen

(T) - difference from control associated with T.I.D. regimen

	T.I.D.	H.S.	Total
AM	14.9	95.2	110.1
PM	41.5	31.1	72.6
Total	56.4	126.3	182.7

Analysis of Variance

<u>Source of variation</u>	<u>df</u>	<u>ss</u>	<u>ms</u>	<u>F</u>
Patients	7	1261.54	180.22	8.15
Sequence	1	14.45	14.45	0.65
Treatment (HS or TID)	1	152.69	152.69	6.90 *
Time (AM or PM)	1	43.95	43.95	1.99
Treatment X Time	1	257.08	257.08	11.63 *
Residual	20	441.90	22.10	1.00

* $p < 0.05$

TABLE 6C: Diastolic blood pressure - sitting position

AM

<u>Treatment A</u>	<u>Control^a</u>	<u>First 4 weeks^b</u>	<u>Second 4 weeks^b</u>
Patient #1	86.7	85.3	95.0
#4	80.3	75.5	80.7
#9	83.7	80.8	80.6
#10	87.3	76.4	80.8
Mean	84.5	79.5	84.3
± S.E.M.	±1.4	±2.0	±3.1

Treatment B

Patient #3	97.0	99.3	98.3
#5	100.3	96.0	88.3
#6	68.7	69.3	60.8
#8	80.7	76.9	73.0
Mean	86.7	85.4	80.1
± S.E.M.	±6.4	±6.3	±7.2

PM

<u>Treatment A</u>	<u>Control^a</u>	<u>First 4 weeks^b</u>	<u>Second 4 weeks^b</u>
Patient #1	84.3	85.1	83.7
#4	82.7	81.0	79.3
#9	84.3	80.7	81.3
#10	87.3	86.0	83.8
Mean	84.7	83.2	82.0
± S.E.M.	±0.8	±1.2	±0.9

Treatment B

Patient #3	101.3	98.2	102.7
#5	90.3	94.7	96.4
#6	70.3	64.0	62.9
#8	77.0	76.9	74.5
Mean	84.7	83.5	84.1
± S.E.M.	±6.0	±6.9	±8.1

^a Average of the measured diastolic blood pressures for the 2-week period (weeks 1 and 2) prior to the crossover trial

^b Average of the measured diastolic blood pressures for the first (weeks 3-6) or second (weeks 7-10) 4-week period of the trial

TABLE 6D: Difference in diastolic blood pressure between treatment and control period for the sitting position

Sequence	Patient number								Total	
	I	3	4	5	6	8	9	10		
Ist AM	1.4 (H)	-2.3 (T)	4.8 (H)	4.3 (T)	-0.6 (T)	3.8 (T)	2.9 (H)	10.9 (H)	25.2	36.1
Ist PM	-0.8 (H)	3.1 (T)	1.7 (H)	-4.4 (T)	6.3 (T)	0.1 (T)	3.6 (H)	1.3 (H)	10.9	
2nd AM	-8.3 (T)	-1.3 (H)	-0.4 (T)	12.0 (H)	7.9 (H)	7.7 (H)	3.1 (T)	6.5 (T)	27.2	40.1
2nd PM	0.6 (T)	-1.4 (H)	3.4 (T)	-6.1 (H)	7.4 (H)	2.5 (H)	3.0 (T)	3.5 (T)	12.9	
Total	-7.1	-1.9	9.5	5.8	21.0	14.1	12.6	22.2	76.2	

(H) - difference from control associated with H.S. regimen

(T) - difference from control associated with T.I.D. regimen

	T.I.D.	H.S.	Total
AM	6.1	46.3	52.4
PM	15.6	8.2	23.8
Total	21.7	54.5	76.2

Analysis of variance

<u>Source of variation</u>	<u>df</u>	<u>ss</u>	<u>ms</u>	<u>F</u>
Patients	7	185.88	26.55	1.76
Sequence	1	0.5	0.5	0.03
Treatment (HS or TID)	1	33.62	33.62	2.23
Time (AM or PM)	1	25.26	25.26	1.67
Treatment X Time	1	70.81	70.81	4.69 *
Residual	20	301.78	15.09	1.00

* $p < 0.05$

TABLE 6E: Systolic blood pressure - standing position

AM

<u>Treatment A</u>	<u>Control</u> ^a	<u>First 4 weeks</u> ^b	<u>Second 4 weeks</u> ^b
Patient #1	152.0	138.4	147.7
#4	134.7	121.8	134.5
#9	120.0	118.2	119.6
#10	135.7	116.4	128.8
Mean	135.6	123.7	132.7
± S.E.M.	±5.7	±4.4	±5.1

Treatment B

Patient #3	152.3	167.8	156.7
#5	155.0	151.8	136.5
#6	135.7	129.5	117.3
#8	137.0	127.3	117.8
Mean	145.0	144.1	132.1
± S.E.M.	±4.4	±8.4	±8.1

PM

<u>Treatment A</u>	<u>Control</u> ^a	<u>First 4 weeks</u> ^b	<u>Second 4 weeks</u> ^b
Patient #1	150.0	151.3	152.2
#4	140.3	134.5	126.2
#9	128.7	122.7	122.5
#10	136.0	133.8	133.3
Mean	138.8	135.6	133.6
± S.E.M.	±3.9	±5.1	±5.7

Treatment B

Patient #3	158.0	162.0	169.2
#5	159.3	146.4	155.3
#6	139.7	135.8	126.4
#8	138.7	124.0	121.3
Mean	148.9	142.1	143.1
± S.E.M.	±4.9	±7.0	±10.0

^a Average of the measured systolic blood pressures for the 2-week period (weeks 1 and 2) prior to the crossover trial

^b Average of the measured systolic blood pressures for the first (weeks 3-6) or second (weeks 7-10) 4-week periods of the trial

TABLE 6F: Difference in systolic blood pressure between treatment and control period for the standing position

		Patient number								
Sequence		I	3	4	5	6	8	9	10	Total
AM		13.6	-15.5	12.9	3.2	6.2	9.7	1.8	19.3	51.2
Ist		(H)	(T)	(H)	(T)	(T)	(T)	(H)	(H)	
PM		-1.3	-4.0	5.8	12.9	3.9	14.7	6.0	2.2	40.2
		(H)	(T)	(H)	(T)	(T)	(T)	(H)	(H)	
AM		4.3	-4.4	0.2	18.5	18.4	19.2	0.4	6.9	63.5
2nd		(T)	(H)	(T)	(H)	(H)	(H)	(T)	(T)	
PM		-2.2	-11.2	14.1	4.0	13.3	17.4	6.2	2.7	44.3
		(T)	(H)	(T)	(H)	(H)	(H)	(T)	(T)	
Total		14.4	-35.1	33.0	38.6	41.8	61.0	14.4	31.1	199.2

(H) - difference from control associated with H.S. regimen

(T) - difference from control associated with T.I.D. regimen

	T.I.D.	H.S.	Total
AM	15.4	99.3	114.7
PM	48.3	36.2	84.5
Total	63.7	135.5	199.2

Analysis of variance

<u>Source of variation</u>	<u>df</u>	<u>ss</u>	<u>ms</u>	<u>F</u>
Patients	7	1425.27	203.61	8.97
Sequence	1	8.41	8.41	0.37
Treatment (HS or TID)	1	161.10	161.10	7.09 *
Time (AM or PM)	1	28.50	28.50	1.25
Treatment X Time	1	288.00	288.00	12.68 *
Residual	20	454.28	22.71	1.00

* $p < 0.025$

TABLE 6G: Diastolic blood pressure - standing position

AM

<u>Treatment A</u>	<u>Control</u> ^a	<u>First 4 weeks</u> ^b	<u>Second 4 weeks</u> ^b
Patient #1	88.0	85.1	93.6
#4	81.0	75.5	81.0
#9	81.7	80.5	82.0
#10	82.0	75.8	80.8
Mean	83.2	79.2	84.4
± S.E.M.	±1.4	±2.0	±2.7

Treatment B

Patient #3	100.7	102.7	106.3
#5	96.7	97.6	89.7
#6	74.3	69.8	63.1
#8	81.0	78.7	70.7
Mean	88.2	87.2	82.5
± S.E.M.	±5.4	±6.7	±8.4

PM

<u>Treatment A</u>	<u>Control</u> ^a	<u>First 4 weeks</u> ^b	<u>Second 4 weeks</u> ^b
Patient #1	87.3	87.6	88.4
#4	79.3	78.8	76.3
#9	85.0	81.6	83.0
#10	82.7	80.8	81.7
Mean	83.6	82.2	82.4
± S.E.M.	±1.5	±1.6	±2.2

Treatment B

Patient #3	101.3	100.7	105.2
#5	93.7	92.0	97.7
#6	71.0	69.6	64.7
#8	81.3	77.1	75.7
Mean	86.8	84.9	86.1
± S.E.M.	±5.8	±6.1	±8.3

^a Average of the measured diastolic blood pressures for the 2-week period (weeks 1 and 2) prior to the crossover trial

^b Average of the measured diastolic blood pressures for the first (weeks 3-6) or second (weeks 7-10) 4-week periods of the trial

TABLE 6H: Difference in diastolic blood pressure between treatment and control period for the standing position

		Patient number								
Sequence		I	3	4	5	6	8	9	I0	Total
Ist	AM	2.9 (H)	-2.0 (T)	5.5 (H)	-0.9 (T)	4.5 (T)	2.3 (T)	1.2 (H)	6.2 (H)	19.7
	PM	-0.3 (H)	0.6 (T)	0.5 (H)	1.7 (T)	1.4 (T)	4.2 (T)	3.4 (H)	1.9 (H)	13.4
2nd	AM	-5.6 (T)	-5.6 (H)	0 (T)	7.0 (H)	11.2 (H)	10.3 (H)	-0.3 (T)	1.2 (T)	18.2
	PM	-1.1 (T)	-4.9 (H)	3.0 (T)	-4.0 (H)	6.3 (H)	5.6 (H)	2.0 (T)	1.0 (T)	7.9
Total		-4.1	-11.9	9.0	3.8	23.4	22.4	6.3	10.3	59.2

33.1

26.1

(H) - difference from control associated with H.S. regimen
(T) - difference from control associated with T.I.D. regimen

	T.I.D.	H.S.	Total
AM	-0.8	38.7	37.9
PM	12.8	8.5	21.3
Total	12.0	47.2	59.2

Analysis of variance

Source of variation	df	ss	ms	F
Patients	7	252.72	36.10	4.9
Sequence	1	1.53	1.53	0.2
Treatment (HS or TID)	1	8.61	8.61	1.2
Time (AM or PM)	1	38.72	38.72	5.3 *
Treatment X Time	1	59.95	59.95	8.1 **
Residual	20	147.25	7.36	1.0

* $p < 0.05$

** $p < 0.01$

TABLE 6I: Systolic blood pressure - supine position

AM

<u>Treatment A</u>	<u>Control</u> ^a	<u>First 4 weeks</u> ^b	<u>Second 4 weeks</u> ^b
Patient #1	156.7	146.2	158.0
#4	141.3	133.3	140.8
#9	130.0	121.5	122.0
#10	142.3	128.0	132.5
Mean	142.6	132.3	138.3
± S.E.M.	±4.7	±4.5	±6.6

Treatment B

Patient #3	165.3	171.0	171.3
#5	159.3	154.4	143.3
#6	134.7	129.3	118.7
#8	143.7	131.3	123.3
Mean	150.8	146.5	139.2
± S.E.M.	±6.1	±8.6	±10.4

PM

<u>Treatment A</u>	<u>Control</u> ^a	<u>First 4 weeks</u> ^b	<u>Second 4 weeks</u> ^b
Patient #1	143.7	159.1	159.8
#4	147.3	143.0	131.7
#9	133.3	-	123.8
#10	140.0	136.5	132.7
Mean	141.1	146.2	137.0
± S.E.M.	±2.6	±5.5	±6.8

Treatment B

Patient #3	158.3	156.8	165.8
#5	162.3	154.7	162.3
#6	132.3	133.8	134.4
#8	141.0	131.6	125.0
Mean	148.5	144.2	146.9
± S.E.M.	±6.2	±5.8	±8.8

^a Average of the measured systolic blood pressures for the 2-week period (weeks 1 and 2) prior to the crossover trial

^b Average of the measured systolic blood pressures for the first (weeks 3-6) or second (weeks 7-10) 4-week periods of the trial

TABLE 6J: Difference in systolic blood pressure between treatment and control period for the supine position

Sequence	Patient number								Total	
	I	3	4	5	6	8	9	10		
AM	10.5 (H)	-5.7 (T)	8.0 (H)	4.9 (T)	5.4 (T)	12.4 (T)	8.5 (H)	14.3 (H)	58.3	67.7
1st PM	-15.4 (H)	1.5 (T)	4.3 (H)	7.6 (T)	-1.5 (T)	9.4 (T)	- (H)	3.5 (H)	9.4	
AM	-1.3 (T)	-6.0 (H)	0.5 (T)	16.0 (H)	16.0 (H)	20.4 (H)	8.0 (T)	9.8 (T)	63.4	86.1
2nd PM	-16.1 (T)	-7.5 (H)	15.6 (T)	0 (H)	-2.1 (H)	16.0 (H)	9.5 (T)	7.3 (T)	22.7	
Total	-22.3	-17.7	28.4	28.5	17.8	58.2	26.0	34.9	153.8	

(H) - difference from control associated with H.S. regimen

(T) - difference from control associated with T.I.D. regimen

	T.I.D.	H.S.	Total
AM	34.0	87.7	121.7
PM	33.3	-1.2	32.1
Total	67.3	86.5	153.8

Analysis of variance

<u>Source of variation</u>	<u>df</u>	<u>ss</u>	<u>ms</u>	<u>F</u>
Patients	7	7264.43	1037.78	-3.69
Sequence	1	10.92	10.92	-0.04
Treatment (HS on TID)	1	11.89	11.89	-0.04
Time (AM or PM)	1	258.97	258.97	-0.92
Treatment X Time	1	231.51	231.51	-0.82
Residual	19	-5345.78	-281.37	1.00

TABLE 6K: Diastolic blood pressure - supine position

AM

<u>Treatment A</u>	<u>Control^a</u>	<u>First 4 weeks^b</u>	<u>Second 4 weeks^b</u>
Patient #1	101.3	89.1	103.3
#4	86.0	78.0	83.7
#9	87.3	82.8	82.4
#10	87.3	77.6	83.7
Mean	90.5	81.9	88.3
± S.E.M.	±3.1	±2.3	±4.3

Treatment B

Patient #3	106.7	106.3	107.0
#5	101.0	96.0	88.7
#6	67.3	70.7	62.7
#8	87.7	81.6	77.8
Mean	90.7	88.7	84.1
± S.E.M.	±7.6	±6.8	±8.1

PM

<u>Treatment A</u>	<u>Control^a</u>	<u>First 4 weeks^b</u>	<u>Second 4 weeks^b</u>
Patient #1	82.3	89.3	88.0
#4	85.0	80.5	78.3
#9	86.3	-	81.8
#10	83.3	83.5	80.3
Mean	84.2	84.4	82.1
± S.E.M.	±0.8	±2.1	±1.8

Treatment B

Patient #3	99.3	98.3	100.2
#5	95.7	89.6	83.7
#6	68.3	67.6	69.6
#8	82.3	80.2	81.5
Mean	86.4	83.9	83.8
± S.E.M.	±6.1	±5.7	±5.5

^a Average of the measured diastolic blood pressures for the 2-week period (weeks 1 and 2) prior to the crossover trial

^b Average of the measured diastolic blood pressures for the first (weeks 3-6) or second (weeks 7-10) 4-week periods of the trial

TABLE 6L: Difference in diastolic blood pressure between treatment and control period for the supine position

Sequence	Patient number									Total	
	I	3	4	5	6	8	9	10			
1st	AM	12.2 (H)	0.4 (T)	8.0 (H)	5.0 (T)	-3.4 (T)	6.1 (T)	4.5 (H)	9.7 (H)	42.5	49.7
	PM	-7.0 (H)	1.0 (T)	4.5 (H)	6.1 (T)	0.7 (T)	2.1 (T)	- (H)	-0.2 (H)	7.2	
2nd	AM	-2.0 (T)	0.3 (H)	2.3 (T)	12.3 (H)	4.6 (H)	9.9 (H)	4.9 (T)	3.6 (T)	35.9	55.0
	PM	-5.7 (T)	-0.9 (H)	6.7 (T)	12.0 (H)	-1.3 (H)	0.8 (H)	4.5 (T)	3.0 (T)	19.1	
	Total	-2.5	0.8	21.5	35.4	0.6	18.9	13.9	16.1	104.7	

(H) - difference from control associated with H.S. regimen
 (T) - difference from control associated with T.I.D. regimen

	T.I.D.	H.S.	Total
AM	16.9	61.5	78.4
PM	18.4	7.9	26.3
Total	35.3	69.4	104.7

Analysis of variance

<u>Source of variation</u>	<u>df</u>	<u>ss</u>	<u>ms</u>	<u>F</u>
Patients	7	295.55	42.22	3.10 *
Sequence	1	0.91	0.91	0.07
Treatment (HS or TID)	1	37.51	37.51	2.76
Time (AM or PM)	1	87.56	87.56	6.44 *
Treatment X Time	1	50.60	50.60	3.72
Residual	19	258.34	13.60	1.00

* $p < 0.025$

TABLE 7: Subjective measurements of side effects derived from questionnaire

- A -Number of patients without symptom
 B -Number of patients with same symptom during each treatment (HS and TID)
 C -Number of patients with new symptom during HS trial
 D -Number of patients whose symptom disappeared during HS trial

Symptom	Number of patients*			
	A	B	C	D
Postural hypotension	2	5	0	1
Drowsiness	1	6	1	0
Weakness	4	2	0	2
Dry mouth	0	8	0	0
Headaches	4	3	1	0
Blurred vision	6	2	0	0
Depression	8	0	0	0
Diarrhea	7	0	1	0
Frequency	8	0	0	0
Impaired sexual activity	8	0	0	0

* Based on frequency of affirmative/negative answers

TABLE 8: Volunteered side effects

PATIENT NUMBER	COMPLAINT	REGIMEN
1	Unable to fall asleep	HS
	Feels more energetic and wakes up more rested	HS
	Not sleeping well	TID
3	Sleeping well but having difficulty getting up	HS
	Nausea (similar to motion sickness)	TID
4	Not sleeping well at night, tossing and turning	HS
	Feels wide awake	TID
	Stomach cramps	TID
5	Nausea (similar to motion sickness)	TID
	Constipated	TID
	Not sleeping well	HS
	Nervous after taking 3 pills at night; palpitations	HS
6	Nausea	TID
	Felt head pounding	HS

TABLE 9: Systolic and diastolic blood pressures
for drop-out patients

<u>PATIENT #2</u>		<u>AM</u>	<u>PM</u>
Sitting	Control	$\frac{127.6}{79.6}$	$\frac{124.7}{80.7}$
	HS	$\frac{122.6}{80.0}$	$\frac{125.3}{77.3}$
Standing	Control	$\frac{137.7}{87.7}$	$\frac{125.6}{82.3}$
	HS	$\frac{134.6}{84.0}$	$\frac{129.3}{78.7}$
Supine	Control	$\frac{131.3}{80.7}$	$\frac{121.7}{76.7}$
	HS	$\frac{131.3}{82.0}$	$\frac{118.0}{76.7}$
<u>PATIENT #7</u>		<u>AM</u>	<u>PM</u>
Sitting	Control	$\frac{141.3}{64.3}$	$\frac{141.7}{66.7}$
	HS	$\frac{138.7}{68.7}$	$\frac{148.7}{70.7}$
Standing	Control	$\frac{130.0}{64.0}$	$\frac{130.7}{65.3}$
	HS	$\frac{136.7}{60.7}$	$\frac{129.3}{68.7}$
Supine	Control	$\frac{145.0}{75.3}$	$\frac{151.0}{74.7}$
	HS	$\frac{148.7}{76.0}$	$\frac{151.3}{81.7}$

TABLE 10: Pill counts

Patient number	Number of pills missed	Total number of pills to be taken	Compliance Factor* Per cent
I	4	252 ^a	98.4
3	4	294 ^b	98.6
4	0	336	100.0
5	2	336	99.4
6	1	294 ^b	99.7
8	7	336	97.2
9	3	588 ^c	99.5
10	7	336	<u>97.2</u>
Mean			98.8
± S.E.M.			1.0

* compliance factor (per cent) = $100 - \frac{\text{number missed}}{\text{total}} \times 100$

^a Not available for last 2 weeks of trial

^b Not available for last week of trial

^c Taking 500 mg T.I.D.; not available for last week of study

TABLE II: "MISSED PILL" COUNTS

Patient number	Number of pills missed	
	Placebo	Treatment
I	3	I
3	I	3
4	-	-
5	2	-
6	-	I
8	4	3
9	-	3
IO	<u>5</u>	<u>2</u>
Total	15	13

TABLE 12: Time interval estimated*
from previous dose time to plasma
sampling of methyldopa

Patient Number	Time (minutes)									
	Control Weeks		TID Weeks				HS Weeks			
3	95	45	195	105	105	110	-	105	100	-
4	85	75	85	65	70	125	100	85	85	60
5	165	175	150	160	200	-	170	200	180	165
8	145	140	585**	-	80	150	150	140	115	165
10	100	130	150	80	75	110	115	100	130	-
Mean ±S.E.M.	115.5 ±39.8		118.5 ±41.3				127.4 ±38.0			

* Time interval estimated from patient-
medication interview at each clinic visit

** This value excluded

Table I3: Plasma methyldopa (ug/mL)* determinations

Patient Number	Control Weeks		TID Weeks				HS Weeks			
3	1.3	1.1	0.9	1.0	0.7	0.3	-	0.8	0.4	-
4	0.6	0.9	0.5	0.5	0.7	0.7	0.4	0.3	0.7	0.4
5	0.9	0.8	1.0	0.9	0.7	-	0.9	0.4	0.7	0.4
8	0.7	0.9	0.3	-	0.7	0.9	0.7	0.8	0.4	0.7
10	0.3	0.4	0.4	0.3	0.4	0.5	0.4	0.6	0.5	-
Mean ±S.E.M.	0.79 ±0.29		0.62 ±0.24				0.56 ±0.18			

* Estimated from the curve of optical density versus concentration (Appendix F)

TABLE I4: Plasma renin activity (PRA) measurements*

Patient Number	PRA (ng/ml/hr)	
	HS	TID
3	-	2.2
4	1.3	1.0
5	1.4	-
8	0.9	1.0
10	-	1.5
Mean ±S.E.M.	1.2 ±0.2	1.4 ±0.5

* Measured at Biochemistry Laboratory, Ottawa General Hospital; assumed patient active for approximately 2 hours.

CHAPTER IV

DISCUSSION

This clinical study is an important one because it demonstrates that a relatively complex medication regimen can be simplified without compromising effectiveness. It also adds support to a previous study on once daily dosing of methyldopa.²⁵⁶

This study was designed as a double-blind, crossover trial. However, it must be pointed out that patients were randomly assigned to the two treatment schedules only after a certain degree of selectivity had been exerted. Due to physician preference and approval, and patient acceptability of the terms of the study, only selective patients were in fact admitted to the study and then assigned to the treatment groups. This lack of complete randomization may have resulted in a patient sample not completely representative of the hypertensive population. In particular, patients with more reliable compliance were preferred.

It can be further argued that this patient population was not completely representative of the hypertensive population for several reasons. Firstly, seven of the 8 patients were females. In the study reported by the Hypertension Detection and Follow-up Program Cooperative Group,³⁰¹ it was found that the hypertensive disease in white females was less severe than in white men, black men or black women and that the white female group was more easily controlled. This patient sample may therefore be subject to less dramatic changes with alterations in therapy. Secondly, seven of the 8 patients were taking methyldopa 250 mg three times a day, in addition to diuretic therapy. Satisfactory response to this regimen might suggest mild hypertensive disease and less

likely to be influenced by changes in therapy. Thirdly, the diagnosis of hypertension was based on their medical history. According to their medical history, these patients were considered hypertensive because their blood pressure was consistently greater than 160/95 mm Hg. At that time, diuretic therapy plus methyldopa was required to maintain their blood pressure at less than 160/95 mm Hg. At the time of entry to the study, the baseline blood pressure level of these patients could not be determined as withdrawal of therapy did not seem justified. Therefore, from their past medical history, it could only be assumed that these patients were still hypertensive. All patients were thought to be essential hypertensives based on their positive response to therapy. None had developed secondary complications. However, one patient was on digoxin and may have developed congestive heart failure as a complication of her hypertensive disease. Fourthly, this patient sample may represent a specific group of patients who are concerned enough about their medical problems to attend regularly a medicine centre. This may also reflect a very compliant group. In light of these considerations, this patient sample is not homogenous, consisting largely of females, and may only be representative of a mild hypertensive female population attending regularly a medicine centre for follow-up.

Two patients, patient #3 and patient #5, should be discussed separately since they were admitted to the study with elevated blood pressure measurements. Justification for their admission to the study is therefore warranted.

Patient #3 did not in fact meet admission criteria in that his baseline blood pressure was not within the range

of defined controlled blood pressure. However, the attending physician requested that he be allowed to participate in the study in order to further assess his response to methyldopa. He had been on methyldopa 750 mg daily for many months. An increase of methyldopa to 1000 mg daily did not further decrease the blood pressure. Some problem with compliance was suspected and this also made him a poor candidate for the study as good compliance was being sought. Despite his elevated blood pressure on admission to the study, his data were included in the analysis since differences in pressures were being analyzed rather than absolute values of blood pressure. His results were consistent with the trend noticed in the other patients. Furthermore, from the pill counts, the estimated compliance factor for this patient was 98.6 per cent. Nevertheless, patient #3 may not represent the group defined for this study.

Patient #5 also had an elevated blood pressure reading on admission to the study though previous review of the medical chart had indicated a controlled blood pressure. This discrepancy was discussed with the attending physician who reassured me that the patient was generally well controlled on the present regimen of methyldopa. A major problem with this patient was that her arm circumference was larger than normal for a person of her stature. For adults, the cuff utilized for measurement of blood pressure must be at least 12 cm wide and for best results should be 20 per cent wider than the diameter of the arm.²⁸⁵ In obese patients, there appears to be an overreading of pressure with increasing arm diameter beyond

20 cm and correcting tables are available.²⁸⁷ The cuff used in the study was 14.2 cm but was probably not appropriate for accurate measurement of blood pressure in this patient.

Nevertheless, because differences were analyzed rather than absolute values, it seemed appropriate to admit the patient to the study and to present the measured blood pressure values and not the corrected values. Some inaccuracy may be incurred by using an inappropriate cuff.

The mean arterial pressure was significantly lower while on the single dosing regimen as compared to the multiple dosing regimen of methyldopa in all positions. In the supine position however, the difference between the two regimens was affected by a difference in the morning and evening blood pressures. Therefore, in the supine position, the significant lowering of the mean arterial pressure observed with the single dosing regimen seems to be solely attributed to its enhanced effect on the morning blood pressure. In the sitting and standing positions, there was a significant lowering of the mean arterial pressure while on the single dosing regimen as compared to the multiple dosing regimen. The contribution of the time of measurement of blood pressure did not appear significant in the standing position. Therefore, the difference observed can probably be attributed to the treatment regimen, though a difference in their effect of the morning and evening blood pressures was also observed. The effect of the single dosing regimen on blood pressure was most evident in the sitting and standing position. This

May be explained by the fact that methyldopa has a greater hypotensive effect in the upright positions than in the recumbent position.²⁶⁴

It was anticipated that a large single dose in the evening might conceivably produce a larger decrease in morning blood pressures but whether the blood pressure lowering effect would be sustained throughout the day was not known. This study confirmed that evening blood pressures were similar while on both regimens. Normally, blood pressure regulation exhibits a circadian rhythm with morning pressures being higher than evening pressures. The multiple dosing regimen does not seem to alter this rhythm. The single dosing regimen, by decreasing morning blood pressure more extensively, may be advantageous since the greatest increase in blood pressure occurs on awakening, with maximum blood pressure rise occurring at 10 00 hours.²¹⁹

The efficacy of the single evening dose regimen of methyldopa might suggest that the pharmacological half-life of methyldopa is much longer than the plasma chemical half-life. The prolonged duration of effect of single evening dosing may be explained by suggesting that the hypertensive disease process in this group of patients might have been altered by previous effective antihypertensive therapy. It has been observed that normal pressures in hypertensive patients persist for variable lengths of time after discontinuation of antihypertensive therapy.

This single dosing regimen's lowering effect of the mean arterial pressure was related to a significant lowering of the systolic blood pressure only. In clinical practice, the diastolic pressure is usually considered more important in the management of blood pressure elevations and the greater decrease in systolic blood pressure alone may not be clinically significant.

The hypotensive effect of methyldopa, particularly in the morning, was greater while on the single dosing regimen as compared to multiple dosing. It may be that higher single doses may be saturating the sulfation of methyldopa which occurs on first pass through the liver and that a greater fraction of the total dose is being made available to the central nervous system. Studies looking at the urinary excretion of metabolites, especially the sulfate conjugate which accounts for 64 per cent of the urinary metabolites,²⁵⁷ might elucidate this issue.

Though more doses were missed than confessed by the patients, the average compliance factor estimated was greater than 98 per cent. As has previously been suggested,²⁹²⁻⁵ patients often do not accurately report drug consumption patterns when queried because of embarrassment, forgetfulness or fear of recrimination.

Pill counts are probably the most commonly employed compliance measure. Although they are inexpensive, objective and easy to implement, pill counts cannot be used with certainty. An inherent assumption of pill counting is that missing doses were consumed by the patient. This usually is true but there are other possible reasons for the presence or absence of dosage units. Further, this measure does not establish that the appropriate number of doses was consumed each day or at the appropriate time intervals.

A more objective method for measuring compliance might be urine assays of methyldopa.^{227,296} but it also cannot be used with certainty as ingestion of methyldopa 24 to 48 hours prior to the test would also yield a positive result.²²⁷ It is difficult from the results obtained to show that single dosing of methyldopa improved compliance, particularly when

the crossover trial of this study made the patients' regimen more complex. Based on the proven efficacy of the single bedtime dosing regimen, it can only be suggested that compliance may be improved.

The incidence of side effects was estimated from a crude comparison of affirmative and negative answers to a standard questionnaire. From the study, the incidence of side effects seemed similar for both regimens. A noticeable difference in side effects with these two regimens may only be observable in patients who are starting methyldopa therapy. Sedation appears in 25 per cent of patients initially taking the drug but tends to become less of a problem after a week of therapy.²⁹⁶⁻²⁹⁹ It may be that the patients in the study were not particularly bothered by this side effect and did not allow a difference to be noticed in the comparison of the two regimens.

With a standardized check-list of side effects, there is a possibility of underreporting, owing, among other factors, to the patient's positive attitude towards the investigator. In many trials, only new symptoms occurring during the treatment have been registered as an expression of side effects.

The two patients who withdrew from the study due to side effects had been assigned to treatment schedule A, that is, single dosing for the first four weeks of the crossover trial then multiple dosing for the last four weeks. Patient #2 described a sensation in her legs similar to a dull cramp

but persistent and unbearable. This patient also complained of feeling heavily sedated and unrested in the morning. As methyldopa does produce sedation in 28.1 per cent of patients and sleep disturbances in 3.8 per cent,³⁰⁰ it is possible that these side effects were related to the administration of a large single dose. Patient #7 complained of a "pounding sensation" in the head and of palpitations. Headaches and palpitations associated with methyldopa therapy have occurred in 8.6 per cent and 0.5 per cent respectively of patients.³⁰⁰ This patient also suffered from emphysema and may have suffered an exacerbation of this condition. It is difficult to ascertain the cause of these side effects though administration of a large dose of methyldopa cannot be ruled out. That both drop-out patients were on the total evening dose regimen at the time alerts to the fact that single daily dosing of methyldopa may not be suitable in all patients.

The plasma methyldopa levels obtained are comparable to other reports.²⁶⁰ No difference in the plasma methyldopa level between the two regimens could be determined. The levels appeared to be similar while on both regimens though the standard error was quite large. A lower plasma level while on single dosing might suggest a greater central penetration of methyldopa and might support a central mechanism of action. A lower plasma level while on multiple dosing might suggest greater peripheral metabolism and might support the mechanism of an active metabolite. The

limitations of the assay used in this study did not permit analysis of the plasma levels obtained while on two different regimens.

The plasma methyldopa determinations reflect both unconjugated and conjugated methyldopa and methyldopamine. It has been suggested that, after repeated oral doses, there is significant enterohepatic circulation and reabsorption of methyldopa.²⁷¹ This may possibly occur with large single oral doses and in light of this, interpretation of plasma methyldopa levels is difficult. Most of these patients have been on methyldopa for more than 6 months. It is probable that these levels represent mostly conjugated methyldopa and methyldopamine, since after long-term oral administration, 60 per cent of chemically determined methyldopa in plasma is in conjugated form.²⁶³

No significant relationship between plasma methyldopa levels and blood pressure control has been reported.²⁶⁰ It would seem that blood pressure determinations are a more precise measure of therapeutic activity of methyldopa than serum concentrations.

Methyldopa is reported to decrease renin activity in normo- and hyperreninemic patients. Measurement of plasma renin activity following each four week period of the crossover trial confirmed that the patients were normoreninemic and did not reveal a difference between the two regimens. As the patients had been receiving methyldopa for some time, any effect of the regimen on plasma renin

activity could not be readily observed.

In conclusion, it would seem appropriate to recommend total evening dose regimens of methyldopa in those patients previously maintained on a "three-times-a-day" regimen in an attempt to simplify drug therapy and to encourage better patient compliance.

The present study adds support to a previous study on once daily dosing of methyldopa.²⁵⁶ However, in addition to comparing blood pressure and side effects, the present study attempted to measure plasma methyldopa and plasma renin activity levels.

In the study by Wright et al., patients were randomly assigned to two treatment schedules and also allocated to three different groups receiving total daily doses of 0.375, 0.75 and 1.5 G methyldopa. The treatment schedules consisted of a 12-week period on either regimen. The sample population of essential hypertensives was larger than the present study and consisted of 17 patients. The population was similar with ages ranging from 48 to 71 years and with a history one to 20 years duration of hypertension. Of these, 3 patients dropped out of the study because of poor compliance or development of intolerable side effects. Similarly, in the present study, there were 2 drop-outs due to intolerable side effects.

The duration of the study was 24 weeks compared to 10 weeks and the longer duration may have allowed for a better assessment of the long-term efficacy of single daily dosing of methyldopa. Though the patients were observed for 3 months prior to the initiation of the study, no baseline blood pressure levels are given. The two-week observation period in the present study attempted to provide a representative base-

line blood pressure and minimize the possible influence of enhanced attentiveness to the patient on blood pressure measurements.

Patients were seen every four weeks and at each of these visits, the blood pressure was measured in the recumbent and erect positions, at 0800, 1200, 1600 and 2000 hours. This 12-hour observation period possibly allowed for a better assessment of the daily variation in blood pressure on each regimen. In the present study, only two daily readings, morning and evening, were obtained but patients were seen more frequently, that is, once a week. By measuring the blood pressure one week after initiation of the new regimen and every week thereafter for 4 weeks, the acute and short-term effects of the new regimen could be observed. Though it has been observed that normal pressures in hypertensive patients may persist for variable lengths of time after discontinuation of antihypertensive drugs, there have also been reports of rebound hypertension with various antihypertensive drugs, including methyldopa, after abrupt discontinuation of therapy. It is therefore important to closely monitor patients in whom the antihypertensive therapy is altered.

In the study by Wright et al, each dose of methyldopa was packaged individually and labelled with day and time of administration. In an attempt to measure compliance, patients were instructed to return all envelopes with tablets not taken and a pill count was done. In the present study, patients were provided with bottles of tablets in variable amounts recorded by the investigator. The patients were asked to return these bottles at each visit with the explanation that the investigator would provide a new supply of medication at this time. The patients were unsuspecting of the pill counts. They were also provided

with a compliance calendar in an attempt to encourage compliance.

In the previous study, the statistical analysis performed was a paired Student's t-test. In the present study, an analysis of variance for crossover designs was used. Unlike a paired t-test, which compares the means of two groups, in this case T.I.D. and H.S., the analysis of variance allows a test for interaction of different sources of variation. The sources of variation considered were the patients themselves, the sequence of administration (Schedule A or Schedule B), the treatment regimen itself (H.S. or T.I.D.), the time of blood pressure measurement (AM or PM) and the interaction of time and treatment. All other sources of variation that could not be identified were considered in the residual component.

Lastly, in the previous study, elicited symptoms or signs of side effects were reported. In the present study, a questionnaire was used to compare the incidence of specific side effects. Despite the limitations of a check-list, a comparison of side effects and newly elicited side effects were reported.



SUMMARY

This double-blind, crossover trial attempted to determine the effectiveness of single evening versus multiple dosing regimens of methyldopa and to compare the incidence of side effects.

The effectiveness of these dosing regimens was determined by blood pressure measurements in the sitting, standing and supine positions, and in the morning and evening. The results demonstrated that single evening dosing further decreased the baseline blood pressure levels, particularly in the morning. The evening blood pressure measurements on both regimens were comparable, suggesting that the blood pressure lowering effect of single evening dosing persists for up to 24 hours.

A symptom questionnaire was used to qualify side effects. No difference was observed in the incidence of side effects which was quantitatively assessed from the frequency of affirmative and negative answers. Of concern, however, is the fact that both drop-out patients were on the single evening dosing regimen which suggests that single daily dosing of methyldopa may not be suitable in all patients.

The complexity introduced by the crossover trial made it impossible to determine if compliance could be encouraged by a single daily dosing regimen. It can only be assumed that a simplified regimen might encourage better patient compliance.

Measurements of plasma methyldopa levels and plasma renin activity were limited and did not allow analysis to determine if the dosing regimens influenced this parameter. Since a correlation between

plasma levels of methyldopa and blood pressure has not been defined, it seems appropriate to use blood pressure recordings as a measure of efficacy.

In the patients participating in the present study, it was possible to convert from a multiple dosing regimen to a single evening dose regimen without loss of therapeutic benefit. In similar patients, it may also be possible to attempt to simplify their drug therapy regimen without compromise of blood pressure control.

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APPENDIX A-I: CONSENT FORM

This study attempts to compare two dosage regimens of methyldopa, a drug which you are presently taking for treatment of high blood pressure. At all times, you will be taking the same total daily dose of methyldopa as prescribed to you by your physician.

As participant, you are requested to visit the clinic once every week and on the same day each week. The coordinator will take blood pressure measurements. At each of these visits, a blood sample will be taken. This sample is taken to determine the plasma level of methyldopa. Also, on the evening of this visit, the coordinator will come to your home to take another blood pressure measurement.

The study will be of a duration of 10 weeks, and for the duration of the study, the drug, methyldopa, will be provided for you.

Your physician will be available at all times.

_____ has been informed of the study and agrees
(physician)
to your participation in this study.

I, _____, have read the details of
(participant)
the study as outlined above and give my consent to participate in this study.

Signature of participant: _____

Signature of coordinator: _____

Date: _____

APPENDIX A-2: CONSENTEMENT

Cette essai thérapeutique a pour but de comparer deux posologies de méthyldopa, un médicament que vous prenez présentement pour la haute tension artérielle. En tout temps, vous allez prendre la même quantité de ce médicament, tel que prescrit par votre médecin.

Comme participant à l'essai, on vous demandera de venir à la clinique une fois par semaine et au même temps chaque semaine. A ce moment, le coordinateur prendra une mesure de votre tension artérielle. A l'occasion de cette visite, on vous demandera aussi de donner une prise de sang. Ceci est à fin de déterminer la concentration de méthyldopa. De plus, le soir de cette même journée, le coordinateur visitera votre domicile pour mesurer encore votre tension artérielle.

L'essai thérapeutique sera d'une durée de dix semaines et, pour cette période, on vous dispensera le médicament, méthyldopa.

Votre médecin sera disponible en tout temps.

_____ a été informé de l'essai et donne sa
(médecin)
permission pour votre participation.

Ayant lu les détails de l'essai tels que soulignés ci-haut, je _____ donne mon consentement:
(participant)

Signature du participant: _____

Signature du coordinateur: _____

Date: _____

APPENDIX B: MEDICATION HISTORY

Prescription Medications:

- I. _____
2. _____
3. _____
4. _____
5. _____
6. _____
7. _____
8. _____
9. _____
10. _____

Former Prescription Medications:

- I. _____
2. _____
3. _____
4. _____
5. _____

OTC Medications:

- I. Antacids _____
2. Laxatives _____
3. Vitamins _____
4. Cold and cough preparations _____
5. Analgesics _____
6. Antinauseants _____
7. Sleep aids _____
8. Other _____

Dependencies

- I. Smoking _____
2. Alcohol _____
3. Caffeine _____
4. Other _____

SENSITIVITIES

APPENDIX C: WEEKLY RECORD

Patient no: _____

Week no: _____

Date: _____

1. Time of last dose: _____

2. Blood pressure measurements

Time	Sitting		Standing		Supine	
	LA/RA	LA/RA	LA/RA	LA/RA	LA/RA	LA/RA
Average						

3. Weight: _____

4. Subjective measurements (see questionnaire)5. Laboratory measurements

Time of last dose: _____

Time of sampling: _____

Plasma methyldopa _____

Date of test: _____

APPENDIX D-I: PATIENT QUESTIONNAIRE*

1. Since your last visit, have you suffered from unsteadiness, light-headedness, or faintness?
If yes, continue:
 - A. Does the unsteadiness or faintness occur only when you are standing?
 - B. Is the unsteadiness or faintness worse first thing in the morning?
2. Have you often felt sleepy during the day?
How many hours, per 24 hours, do you sleep?
3. Have you noticed weakness in the limbs? Does this interfere with your daily activity?
4. Do you suffer from a dry mouth? Does this interfere with talking or eating?
5. Since your last visit, have you suffered from headaches? At what time of the day do the headaches occur?
6. Have you had blurring of vision since your last visit?
7. Have you been depressed since your last visit? Did you consult a doctor about your depression?
8. Are your bowel movements irregular?
If yes, continue:
 - A. How often do you go?
 - B. Are your motions often loose or liquid?
9. How many times, on the average, do you rise at night to pass urine?
10. During sexual intercourse, are you:
 - A. troubled by failure to maintain an erection?
 - B. troubled by failure to ejaculate?

*Based on a questionnaire employed by Bulpitt and Dollery³⁰¹

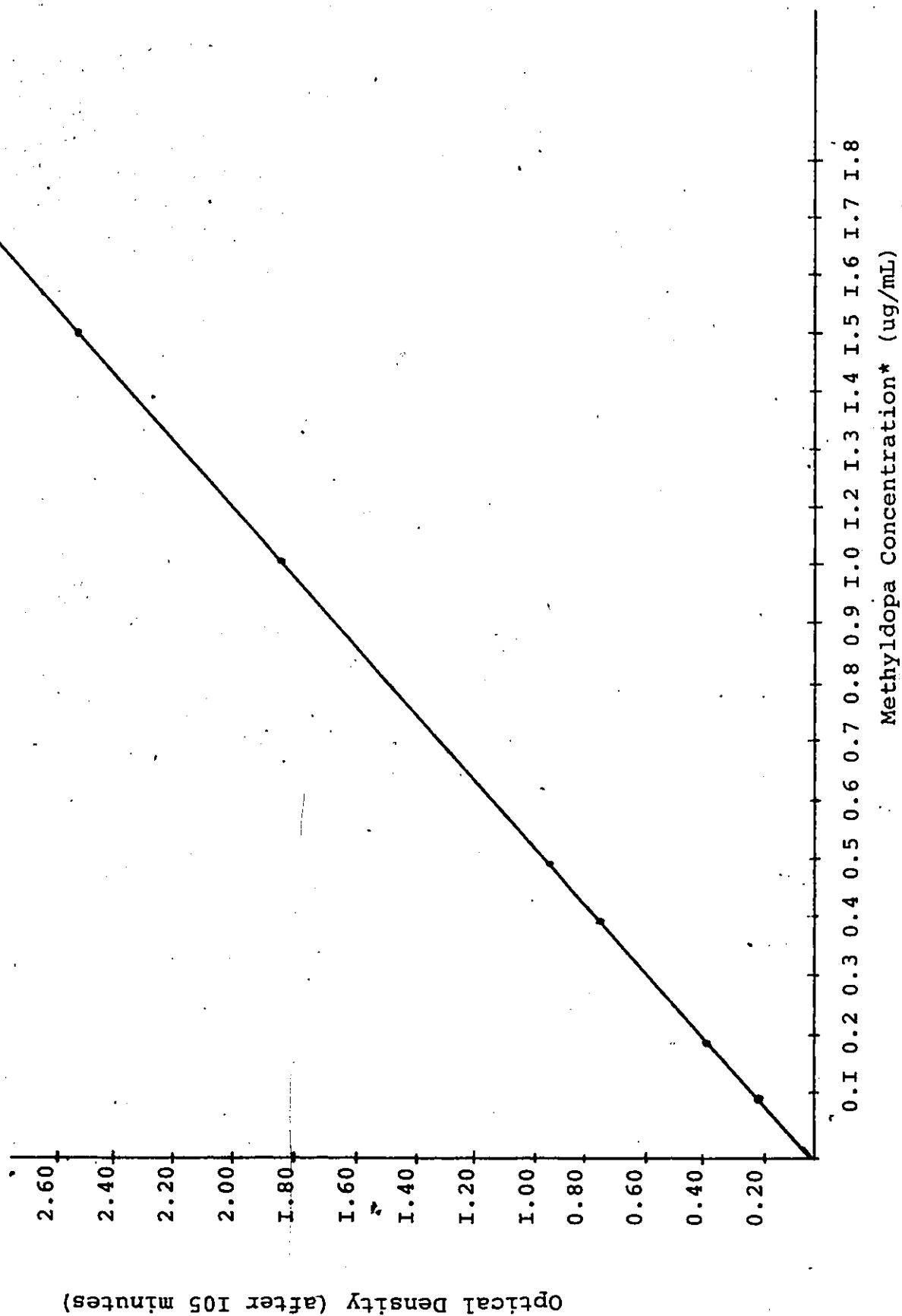
APPENDIX D-2: QUESTIONNAIRE

1. Depuis votre dernière visite, est-ce que vous sentez parfois étourdi(e)? Si oui, continuer:
 - A. Est-ce que vous sentez étourdi(e) seulement lorsque vous êtes debout?
 - B. Est-ce que vous êtes étourdi(e) plus souvent la première chose le matin?
2. Avez-vous la tendance à dormir durant le jour, c'est à dire, est-ce vous êtes souvent assez fatigué(e) pour vouloir dormir le jour?
Combien de sommeil avez-vous, sur la moyenne, par jour?
3. Avez-vous remarqué une faiblesse dans les extrémités, c'est à dire dans vos bras et/ou dans vos jambes?
Est-ce que c'est assez sévère pour interrompre votre routine habituelle?
4. Avez-vous souvent la bouche sèche, c'est à dire peu de salive dans la bouche?
Est-ce que cela affecte votre abilité de parler ou/et de manger?
5. Depuis votre dernière visite, avez-vous souffert de maux de tête?
A quel temps du jour souffrez-vous de ces maux de tête?
6. Depuis votre dernière visite, avez-vous eu de la difficulté avec votre vision?
7. Depuis votre dernière visite, est-ce que vous vous sentez déprimé(e)?
Avez-vous discuté avec votre médecin votre dépression?
8. Avez-vous des selles régulièrement?
Si non, continuer:
 - A. Combien de selles avez-vous par jour?
 - B. Sont-elles molles ou liquides?
9. Sur la moyenne, combien de fois par nuit devez-vous vous lever pour aller à la toilette?
10. Lorsque que vous avez du sexe, avez-vous de la difficulté
 - A. à maintenir une érection?
 - B. à éjaculer?

APPENDIX E: COMPLIANCE CALENDAR

This is for the week starting _____
and ending _____

# tabs.	Sun	Mon	Tues	Wed	Thurs	Fri	Sat
A							
A							
A							
B							

APPENDIX F: METHYLDOPA CONCENTRATION CURVE **

* Corrected for plasma blank

** Derived from triplicate determinations