This work is a thesis submitted for the degree of Doctor of Philosophy in the Australian National University.

TITLE:

ACTIVITY OF THE SYMPATHETIC NERVOUS SYSTEM AND RENIN-ANGIOTENSIN SYSTEM IN ESSENTIAL HYPERTENSION

This thesis is my own original work.

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CHAPTER 1
INTRODUCTION

This thesis reports a series of studies in which I have examined some facets of hypertension. The pathophysiology of hypertension has been investigated from the point of view of disordered sympathetic nervous function. The level of excretion in urine of the chemical mediator, noradrenaline, has been used as an index of sympathetic nervous activity. The possibility has been considered that certain subgroups of hypertensive subjects may have an increased level of sympathetic activity at rest, or show an exaggerated sympathetic responsiveness to physiological stimuli such as change in posture, and mental activity.

The potential pathogenicity of such an overactivity of the sympathetic nervous system in hypertension has been considered from the point of view of possible direct and indirect effects on blood pressure. The possibility of a direct relationship between sympathetic nervous activity and blood pressure in hypertension has been investigated by studying, in parallel, noradrenaline and blood pressure levels at rest, and with stimulation of the sympathetic nervous system. The possibility of indirect effects of the sympathetic system on blood pressure has been investigated by studying the relationship of sympathetic activity to the level of the enzyme, renin, in blood plasma. Renin is produced principally by the kidney, and influences blood pressure through its effect on body salt and blood volume.

The clinical significance of overactivity of the sympathetic nervous system has been considered from 2 points
of view. First, the prevalence in a hypertensive population of symptoms suggestive of sympathetic overactivity has been studied, and the relationship of symptoms to assessed levels of sympathetic activity, and to other factors, such as anxiety, has been investigated. Second, a clinical trial of a drug that selectively interferes with a specific receptor of the sympathetic nervous system has been carried out, in order to determine whether the therapeutic response to the drug, in terms of lowering of blood pressure, is related to the level of sympathetic nervous activity in hypertension.

The introductory section of this thesis will review:

1. The variability of blood pressure in essential hypertension, and the possibility that repeated, inappropriately large blood pressure responses, to events which affect sympathetic nervous system activity, may lead eventually to sustained elevation of blood pressure.

2. Evidence of changed sympathetic nervous system activity in some hypertensive subjects as shown by altered secretion of the neurotransmitter, noradrenaline.


4. The role of the sympathetic nervous system, and other factors, in controlling the release of renin.

5. Clinical trials of drugs that block the β-adrenergic receptors of the sympathetic nervous system, and hence
lower blood pressure by mechanisms related to reduced sympathetic activity.

I. VARIABILITY OF BLOOD PRESSURE.

Spontaneous Variability of Blood Pressure

Only since the development of techniques for continuous automatic or semi-automatic measurement of BP (Richardson et al., 1964) has it been possible to study the spontaneous variability of BP in the absence of an observer. Two forms of variation in BP occur: large diurnal changes, BP being at its lowest during sleep, and short-term pressor peaks related to such things as physical activity and emotion.

The spontaneous variability of BP in hypertensive and normotensive subjects has been compared in several studies (Richardson et al., 1964; Bevan et al., 1969). Indices used have been the range of blood pressures, systolic and diastolic during a 24-hour period, which is predominantly a measure of the diurnal change in BP, and the "undulation index" (Bevan et al., 1969) or similar computation, as a measure of short-term variability. From the hospital-based studies of Richardson et al. (1964) and Bevan et al. (1969), it would appear that both the range and short-term variability of BP are greater in hypertensive patients than in subjects with normal blood pressure, and that among essential hypertensives, the range and variability is greatest in borderline hypertension, least in malignant hypertension, and intermediate in mild to moderately severe sustained hypertension. A contrary finding, however, has been reported by Sokolow et al. (1966), in a large study which differed in design from the British studies in that
BP was monitored during the patients' usual routines of work. In this setting, variability of BP in hypertensive patients was found to be unrelated to the grade of severity of the hypertensive disease.

**Blood Pressure Responses to Pressor Stimuli**

Stimuli used experimentally have included change in posture, "mental stress", pain (in the cold pressor test), and exercise. It might be anticipated that the greater "spontaneous" variability of BP in essential hypertension could, perhaps, be paralleled by a greater than normal responsiveness to some or all of these pressor stimuli.

(i) **Head-up tilting.** The cardiovascular response to head-up tilting is complex, and includes an increase in heart rate, a fall in cardiac output, an increase in total peripheral vascular resistance, a small rise in mean BP, and a fall in renal blood flow and glomerular filtration rate (Lee *et al.*, 1966; Frohlich *et al.*, 1967). Overall, the response in essential hypertension is qualitatively and quantitatively similar to that in normal subjects, but the scatter in blood pressure responses is greater in hypertensives, ranging from a substantial BP rise, through to postural hypotension. Patients showing postural hypotension tend to have more severe hypertensive disease. Conversely, a greater than normal rise in BP with tilting, an "orthostatic hypertensive" response, tends to occur in subjects with borderline or mild sustained hypertension. A large rise in total peripheral resistance is the basis of a supranormal BP rise with tilting (Frohlich *et al.*, 1967).
(ii) "Mental Stress". Blood pressure rises occur in anxiety-provoking situations (Nestel, 1969), and even during quiet conversation (Ulrych, 1969). There is an accompanying catecholamine response (Nestel, 1969), predominantly involving adrenaline (von Euler, 1964). The blood pressure rise is primarily related to an increase in cardiac output (Brod, 1959; Ulrych, 1969). The BP response to mental stress in patients with sustained essential hypertension is similar to that in normal subjects (Brod, 1959; Ulrych, 1969). However, a greater than normal BP and catecholamine response to mental stress has been reported in borderline hypertension (Nestel, 1969).

(iii) The Cold-Pressor Test. Early reports of greater than normal blood pressure rises in essential hypertensives stimulated by painful procedures such as the cold pressor test (Hines and Brown, 1932), have not been consistently confirmed. In contrast to the finding that a substantial proportion of essential hypertensives were hyperreators to the cold pressor test (Hines, 1940), Boyer et al. (1960), in a study including borderline and sustained hypertensives, could find no difference between hypertensives and normotensives in the average BP response, or in the proportion of hyperreactors (rise in mean BP more than 20 mmHg) in the 2 groups.

(iv) Exercise. With dynamic exercises, cardiac output rises, total peripheral resistance falls, systolic blood pressure rises, and diastolic blood pressure changes little if at all. In most published studies, the response in essential hypertension has been reported as
qualitatively and quantitatively similar to that in normal subjects (Hamer et al., 1967; Julius and Conway, 1968). Hamer et al. (1967) found similar changes in BP and total peripheral resistance in borderline, moderate sustained, and severe essential hypertension.

In summary, greater than normal pressor responses to tilting and mental stress have been described in borderline hypertension. In sustained essential hypertension, the response to these stimuli, and to the cold pressor test and dynamic exercise, are within normal limits.

The greater than normal BP rise in borderline hypertensives subjected to mental stress is accompanied by an above-average catecholamine response (Nestel, 1969). A neural basis for the supranormal BP response to tilting in "orthostatic hypertensives" also is inferred, although increased vascular reactivity has not been excluded as the possible cause (Frohlich et al., 1967). The relationship of the change in urinary noradrenaline excretion on tilting to the blood pressure response has been assessed (Chapter 3), to investigate further the question of sympathetic nervous responsiveness in patients with an orthostatic hypertensive response.

The Potential Pathogenicity of Repeated Pressor Responses

It is probable that an enhanced sympathetic responsiveness to some pressor stimuli (such as head-up tilting and "mental stress") may be a common accompaniment of borderline and early mild sustained essential hypertension, to be lost later if the hypertensive process becomes more severe (Frohlich et al., 1967; Nestel, 1969). The suggestion that
This enhanced sympathetic responsiveness in borderline hypertension contributes to the development of sustained essential hypertension, and hypertensive cardiovascular complications, is largely speculative, as the evidence is both indirect and incomplete. The first line of evidence relates the origin of the elevated cardiac output in borderline hypertension to the adrenergic responsiveness, and traces the clinical and haemodynamic progression of borderline hypertension to sustained hypertension. The second line of evidence stresses the relationship of the casual blood pressure (and hence reactive changes in BP) to morbidity in essential hypertension.

(i) The relationship of sympathetic hyperresponsiveness to an elevated cardiac output in borderline hypertension. There have been numerous reports documenting the existence of an elevated mean cardiac output, with total peripheral resistance near normal, in borderline essential hypertension (Eich et al., 1966; Julius and Conway, 1968; Conway, 1970). The cardiac output is elevated in only a proportion of borderline hypertensives (Conway, 1970). The haemodynamic findings are in contrast to those of a normal or reduced cardiac output and elevated total peripheral resistance in severe hypertension (Bello et al., 1967). The basis of the above-average cardiac output is incompletely understood. However, studies on the effect of β-adrenergic and parasympathetic blockade on cardiac output in borderline hypertension (Julius et al., 1971) provide some support for the concept that the elevated cardiac output is related to sympathetic nervous overactivity in combination with parasympathetic underactivity.
It is possible that a relationship between sympathetic activity and increased cardiac output could be mediated by an indirect mechanism, through retention of sodium. In susceptible animals, such as the partially nephrectomized dog (Coleman and Guyton, 1969), saline loading produces an elevation in cardiac output and blood pressure. In man, head-up tilting is accompanied by a marked reduction in the urinary excretion of sodium (Birkenhager et al., 1962). In sympathetic hyperresponders, with oft-repeated stimulation, the potential may exist for retention of sodium and possibly resultant elevations in BP and cardiac output. Among hypertensives, cardiac output is highest in hyperresponders to tilt (Frohlich et al., 1967). Birkenhager et al. (1968) found positive correlations between resting cardiac index, blood volume, and variability of BP in untreated essential hypertensives. The acute effect of tilting on the urinary excretion of sodium, in hypertensives with a greater than normal blood pressure response to tilt, is presented in Chapter 4.

It is now clear that progression of borderline hypertension to sustained hypertension commonly occurs (Miall and Lovell, 1967; Heyden et al., 1969). A tendency for haemodynamic status also to change, from a state of high cardiac output and normal total peripheral vascular resistance, to normal cardiac output and high peripheral resistance, has been documented, but the number of patients studied is small (Eich et al., 1966). Cross-sectional studies, on different grades of severity of hypertension, suggest that changes in haemodynamic status do occur (Frohlich et al., 1970). The basis of the rise in total peripheral resistance is not known.
The concept of autoregulation of flow, which refers to adjustments in vascular resistance of an organ in relation to its perfusion, has been implicated, but may not be valid for the body as a whole (Coleman and Guyton, 1969).

(ii) The relationship of casual BP to morbidity in hypertension. It has been suggested by Smirk (1957) that as hypertensive patients spend much of their time sleeping or at rest, the "basal" blood pressure, measured under defined conditions of rest, may provide the best index of prognosis. A close relationship between basal BP, and both the presence of stigmata of hypertensive cardiovascular disease and the prognosis, has been demonstrated (Smirk, 1957). However Hamer (1968) has emphasized that in patients engaged in normal activities, the blood pressure load on the heart and blood vessels during waking hours is probably most closely represented by the casual BP. It might therefore be expected that the risk of developing hypertensive cardiovascular complications be related also to the level of the casual BP. This has been borne out in a large study by Sokolow et al. (1966), on patients engaged in normal routines of work, in which a close relationship was found to exist between the severity of the hypertensive disease (graded on the presence of hypertensive cardiovascular complications) and the average BP recorded continuously by indirect means.

Casual BP reflects in part reactive BP changes (Smirk, 1957). The responsiveness of hypertensives to pressor stimuli might thus be expected to be a determinant of the level of the casual BP. Whether this is so has been little
studied. However, the observation has been made by Hamer et al. (1967) that systolic blood pressure during exercise, in hospitalized patients some of who had a "normal" resting BP at the time of testing, predicted subsequent outpatient casual pressures.

II. URINARY AND PLASMA LEVELS OF CATECHOLAMINES AND THEIR METABOLITES IN ESSENTIAL HYPERTENSION.

3,4-dihydroxyl-benzyl amines (catecholamines) occur normally in urine (Holtz et al., 1947). Urinary adrenaline has its origin in the secretions of the adrenal medulla (von Euler et al., 1954(a)). Noradrenaline is the neurotransmitter of the sympathetic nerves (von Euler, 1946), but is released also from the adrenal medulla (Lund, 1951). The sympathetic nerve endings are thought to be the major source of circulating noradrenaline. This finds support in the failure of bilateral adrenalectomy to suppress the urinary excretion of noradrenaline (von Euler et al., 1957).

With the development of a sensitive method of assay of urinary catecholamines (Lund, 1949), the hypothesis that these pressor amines play an important role in the genesis of essential hypertension could be tested. An elevated total peripheral vascular resistance was a consistent finding in early studies on the haemodynamics in essential hypertension, cardiac output being within normal limits (Pickering, 1936; Wiggers, 1938). Greater amounts of noradrenaline in the urine of hypertensives than in subjects with normal blood pressure would be consistent with the hypothesis that sympathetic nervous system overactivity
underlies the increased peripheral resistance of hypertension.

In several studies, mean excretion rate of catecholamines in essential hypertensives was no different from that in subjects with normal BP (Crout et al., 1961; Theil and Garcia, 1965), but in some investigations, a proportion of hypertensives were found to have an elevated excretion of noradrenaline (von Euler et al., 1954; Goodall and Bogdonoff, 1961; Nestel and Doyle, 1968). The urinary excretion of catecholamines is very labile, being readily influenced by such factors as posture (Sundin, 1956), exercise (Kärki, 1956), and emotion (Levi, 1963). The discrepancies in these findings may well have arisen in part from failure, in some cases, to adequately standardize the experimental conditions.

The major urinary metabolites of adrenaline and noradrenaline are 3-methoxy-4-hydroxymandelic acid (VMA), metadrenaline, and normetadrenaline. Normetadrenaline is principally derived from noradrenaline released at the sympathetic nerve ending, and o-methylated at the nerve ending, or in the liver (Wurtman, 1965). The main source of urinary metadrenaline is adrenaline secreted by the adrenal medulla, and metabolized by catechol-o-methyltransferase in the liver and other organs (Wurtman, 1965). VMA is the urinary metabolite of both adrenaline and noradrenaline (Armstrong et al., 1957), formed from the catecholamines by o-methylation and oxidative deamination. Most studies on the urinary excretion of metadrenaline, normetadrenaline, and VMA in hypertensives have shown the rate of excretion not to differ significantly from that in normotensives.
(Crout et al., 1961; Theil and Garcia, 1965; Gitlow et al., 1960). However, Brunjes (1964) reported low urinary excretion of VMA and metadrenaline in essential hypertension.

Fluorimetric assays of plasma catecholamines have been characterized by poor reproducibility, related to a high plasma blank fluorescence. Recently, 2 sensitive assays for plasma adrenaline and noradrenaline have been developed. In one (Valori et al., 1970), a modification of the trihydroxyindole method of Lund (1949), the problem of background fluorescence has been largely overcome. The other makes use of a double-isotope derivative technique (Engelman et al., 1970). The mean plasma catecholamine level, as measured by these methods, is elevated in essential hypertension (Engelman et al., 1970; De Quattro, 1972).

Interpretation of the higher plasma and urinary levels of noradrenaline in a proportion of essential hypertensive patients is difficult. In the first place, the pathogenesis of the blood pressure elevation certainly involves mechanisms more complex than a sustained vasopressor response involving an increase in total peripheral resistance, and mediated directly through the sympathetic nervous system. Populations of essential hypertensives are not homogeneous in a haemodynamic sense. Although the blood pressure elevation in severe sustained hypertension reflects an increase in total peripheral resistance, in borderline hypertension and mild sustained hypertension TPR is often normal, cardiac output being elevated (Julius and Conway, 1968). The primary abnormality of early hypertension may possibly be an elevation in cardiac output. Perhaps with
progression of the disease to more severe forms, the haemodynamic pattern of a normal cardiac output and increased TPR, long considered typical of essential hypertension, may evolve (Bello et al., 1967). Possible causes of the rise in TPR in severe hypertension, other than increased sympathetic nervous activity, include an increase in vascular reactivity to vasoactive agents (Doyle et al., 1959), and a non-contractile impediment to blood flow (Conway, 1963).

A second major problem in the interpretation of the higher noradrenaline levels centres around the validity of plasma and urinary noradrenaline levels as an index of sympathetic nervous activity. This question is reviewed in more detail in Chapter 2. Difficulties relate particularly to the fact that only a small proportion of the noradrenaline released at sympathetic nerve endings diffuses into plasma; most is "inactivated" locally by reuptake into the nerve ending or by o-methylation (Andén et al., 1969).

In recent years, attempts have been made to classify essential hypertension in terms of certain physiological and clinical characteristics. There have been reports of reduced plasma volume (Tarazi et al., 1968), low plasma renin activity (Jose and Kaplan, 1969), and increased responsiveness of the sympathetic nervous system (Frohlich et al., 1967; Nestel, 1969). Changes in catecholamine production might theoretically be encountered with each of these. Plasma volume is reduced in phaeochromocytoma (Brunjes et al., 1960). The secretion of renin and noradrenaline are related through a common response to salt depletion and hypovolaemia (Vander, 1967). The relationship of urinary catecholamine excretion to plasma
volume, responsiveness of the sympathetic nervous system, and renin-angiotensin status has been studied (Chapter 7).

III. ESSENTIAL HYPERTENSION WITH "HYPERKINETIC CIRCULATION".

Symptoms of episodic palpitations, sweating, and anxiety in patients with an elevated blood pressure should suggest the possible diagnosis of phaeochromocytoma. But the majority of hypertensive patients with such symptoms, when adequately investigated, prove not to have a catecholamine-secreting tumour. Significant discomfort related to recurrent cardiac irregularities, or rapid, forceful cardiac action, occurring without an obvious precipitant, or in relation to exercise or emotion, is a common complaint in these patients (Frohlich, 1971). Findings reported in these hypertensives with "hyperkinetic circulation" include an elevated resting pulse rate and cardiac output (Frohlich et al., 1969), and an increased sensitivity of the β-adrenoceptors of the heart to infused isoprenaline, in hypertensives with "hyperdynamic β-adrenergic disease" (Frohlich et al., 1969).

The term "hyperkinetic circulation" has found wide usage in the literature on essential hypertension, but the meaning remains ill-defined and confusing. Symptomatology, physical findings, and haemodynamic findings have been used to differing extents by different authors in categorizing the syndrome. Cardiac symptoms, a high resting pulse rate and an elevated cardiac output have all been emphasized (Julius et al., 1971; Frohlich, 1971). The limits of the syndrome are not well defined, and the relationship of hypertension with "hyperkinetic circulation" to
"neurocirculatory asthenia" (Hurst and Logue, 1966), and to the "hyperkinetic heart syndrome" (Gorlin, 1962), in which systolic blood pressure is commonly elevated, is not clear. That hypertension with hyperkinetic circulation constitutes a distinct subgroup of essential hypertension is open to question. An elevated resting pulse rate and cardiac output have been reported in borderline and mild sustained essential hypertension in the absence of cardiac symptoms (Eich et al., 1962). Further, it is well known that essential hypertension is commonly asymptomatic at the time of diagnosis, symptoms developing later in relation to anxieties induced by knowledge of the diagnosis and possible complications of hypertension (Pickering, 1972). The symptoms described in hyperkinetic circulation are, in fact, non-specific, and similar to those commonly found in anxiety states (Hurst and Logue, 1966).

The prevalence of symptoms of hyperkinetic circulation in a consecutive series of patients with untreated essential hypertension has been studied (Chapter 8), and the relationship of these symptoms to levels of anxiety and neuroticism, and to the responsiveness of the sympathetic nervous system investigated.

IV. THE CONTROL OF RENIN RELEASE.
Mechanisms Controlling the Secretion of Renin

Controlling influences on the secretion of renin have recently been reviewed by Davis (1971). Current evidence indicates that an intrarenal baroreceptor, the macula densa, the renal sympathetic nerves, and circulating catecholamines may all have an important role. The predominant system
promoting a renin response in a particular situation is
dependent on the experimental conditions.

The "baroreceptor hypothesis" views the sensor as the
juxtaglomerular cells of the afferent arteriole, these cells
responding to a decrease in stretch with an increase in the
secretion of renin (Skinner et al., 1964). Changes in
renal arterial pressure, blood volume, and renal interstitial
pressure, and vasodilator and vasoconstrictor drugs, could
all operate at this level. Attempts have been made to
isolate the effects of the intrarenal baroreceptor by
studying the non-filtering, denervated kidney (Blaine et al.,
1970(a), 1970(b)). With this model, renin responses to
haemorrhage and aortic constriction have been demonstrated
in the dog which could not have been mediated through the
macula densa or sympathetic nerves.

The "macula densa theory" views the macula densa
influencing renin secretion by acting as a sodium sensor.
There is dispute over what constitutes an adequate stimulus
to the macula densa. Vander and Carlson (1969) have
stressed an inverse relationship between the sodium load
delivered to the distal renal tubule and renin release.
Cooke et al. (1970) have presented evidence supporting
a direct relationship between intraluminal sodium
concentration in the distal tubules and renin release.
Confusion in this area may well have arisen from the
extensive use of diuretics as a stimulus. The response
to diuretics is complex, and may involve sodium depletion,
hypovolaemia, altered tubular sodium concentrations,
changes in intrarenal vascular resistance, and possibly
direct effects on the macula densa (Vander and Carlson,
Evidence for the role of the renal sympathetic nerves in the release of renin has come from several sources. Vander (1965) produced release of renin by electrical stimulation of renal nerves in dogs, and by infusion of catecholamines. The renin response to sodium depletion in dogs is abolished by renal denervation (Mogil et al., 1969). Gordon et al. (1967) noted an absent renin response to upright posture and sodium depletion in a patient with autonomic degeneration. Renin secretion accompanies the endogenous release of catecholamines, such as in hypoglycaemia (Otsuka et al., 1970).

Effects of the Sympathetic Nervous System and Circulating Catecholamines on Renin Secretion

(i) Circulating catecholamines. Circulating catecholamines can induce secretion of renin. This has been shown in the dog following catecholamine infusions (Vander, 1965), and release of endogenous catecholamines, in response to insulin hypoglycaemia (Otsuka et al., 1970). Assaykeen et al. (1970) reported the renin response to insulin hypoglycaemia to be abolished by the β-adrenergic receptor blocker, propanolol, but to be little influenced by the α-adrenergic blocking agent, phenoxybenzamine. Isoprenaline leads to small increases in renin secretion in the normal dog (Winer et al., 1971) and to a large renin response in dogs with experimental renovascular stenosis. The response appears to be independent of changes in arterial blood pressure and renal blood flow (Ayers et al., 1969). The mechanism of the renin response to circulating...
adrenaline and noradrenaline has been studied in the dog using the non-filtering kidney model (Johnson et al., 1971). Renin secretion produced by an infusion of adrenaline appears to be related to a reduction in renal blood flow, and is abolished by the vasodilator, papaverine. The effect of circulating noradrenaline seems to be independent of change in renal blood flow.

(ii) Renal sympathetic nerves. Renin secretion follows electrical stimulation of the renal nerves (Vander, 1965), and activation of the sympathetic nervous system by such noradrenergic stimuli as head-up tilting (Oparil et al., 1970). Michelakis and McAllister (1972) noted the renin response to upright posture to be markedly reduced by propanolol, but not affected by phenoxybenzamine. Winer et al. (1969) found the increase in PRA produced by upright posture and diazoxide to be reduced by both propranolol and the α-blocker phentolamine.

(iii) Adrenergic receptors subserving renin release. There is considerable confusion in the published work on renin release as to whether renin secretion produced by sympathetic nervous stimulation and circulating catecholamines is classifiable in terms of classical adrenergic receptor theory. This confusion probably derives in part from the fact that there may be direct effects, on the juxtaglomerular cells (Michelakis et al., 1969), and indirect effects secondary to changes in blood pressure, renal vascular resistance, glomerular filtration rate, and filtered load of sodium passing to the distal renal tubules (Johnson et al., 1971). A second factor may be the use of phentolamine (Winer et al., 1969) as an
α-blocker. This drug has independent effects as a vasodilator (Nickerson, 1965), and might influence renin release independently of its α-blocking activity, by reducing renal vascular resistance. The work of Michelakis and McAllister (1972), and of Assaykeen et al. (1970) suggests that β-receptors mediate the major component of the renin response to sympato-adrenomedullary activation, at least for the stimuli of upright posture and hypoglycaemia. But the matter is not entirely settled (Winer et al., 1971).

**Low-Renin Essential Hypertension**

Plasma renin activity is suppressed and unresponsive in primary aldosteronism. The place of measurement of the plasma renin level in the investigation of cases of suspected primary aldosteronism has been stressed (Conn et al., 1964). But it has become clear that in approximately 20% of essential hypertensives PRA is low during recumbency, and rises with stimuli such as upright posture less than in normal subjects (Channick et al., 1969). An elevated aldosterone secretion rate is not the basis of the suppressed renin release in these patients; in a series of 300 unselected essential hypertensives, Crane et al. (1972) found only 1 in 33 patients with low renin levels had primary aldosteronism.

Although aldosterone levels are normal in low-renin essential hypertension, there is a large body of indirect evidence supporting mineralocorticoid excess as the basis of the disorder. In patients with low-renin essential hypertension, an elevated total body exchangeable sodium (Woods et al., 1969) and expanded extracellular fluid
volume (Jose and Kaplan, 1969) have been reported. Aminoglutethemide, an inhibitor of adrenal steroidogenesis, lowers BP more in these patients than in other essential hypertensives (Woods et al., 1969). Control of the elevated BP by a high dose of spironolactone is achieved in a higher proportion of patients with renin unresponsive hypertension than in hypertensives with normal or elevated PRA (Crane and Harris, 1970). An active search for sodium-retaining hormones other than aldosterone as a possible basis of the disorder continues. Increased secretion of 18-hydroxydesoxycorticosterone has been reported in certain patients with hypertension (Melby et al., 1971). These patients have suppressed plasma renin levels, and respond to high doses of spironolactone with normalization of BP. However, desoxycorticosterone (Woods et al., 1969) and 18-hydroxydesoxycorticosterone (Spark and Melby, 1971) levels have been found to be normal in low-renin hypertension. The possibility of an undiscovered steroid remains.

Although there is strong evidence that the sympathetic nervous system plays an important role in renin release (Gordon et al., 1967), sympathetic activity in low-renin hypertension has been little studied. Crane et al. (1972) have reported low urinary catecholamine levels in this disorder, but suppression of catecholamines could be incidental to the abnormality in sodium status in these individuals with an increased total body exchangeable sodium (Gordon et al., 1967), and not causally related to the low renin level. The finding of Crane and associates contrasts with that of Jose et al. (1970), who noted PRA to be unrelated to urinary catecholamine levels. This
latter group reported also a diminished renin response to noradrenaline infusion in 4 patients with renin unresponsive hypertension, and raised queries as to the sensitivity to catecholamines in this condition.

Underactivity of the sympathetic nervous system could be related to the phenomenon of low-renin essential hypertension. Orthostatic hypotensives, with postural hypotension, and a reduced rise in total peripheral vascular resistance on tilting (Frohlich et al., 1967), could possibly prove to be renin unresponsive. This possibility has been investigated by measuring the plasma renin activity at rest, and the PRA, blood pressure, and catecholamine response to tilting in subjects with untreated essential hypertension (Chapter 4).

V. THE ANTI-HYPERTENSIVE ACTION OF β-ADRENERGIC BLOCKING DRUGS.

Apart from diuretics, most drugs currently used in the treatment of hypertension diminish sympathetic nervous system activity, usually through effects on ganglionic transmission, or more commonly by inhibiting catecholamine uptake, synthesis, storage or release. In general these drugs interfere with the innervation of arterioles and veins, thereby blunting the peripheral vascular responses to change in posture, and accentuating orthostatic fluctuations in BP.

β-adrenergic blockers are exceptional in this respect and several studies, mainly of propranolol, have demonstrated satisfactory control of moderate hypertension, even in the supine position and without undesirable hypotension in relation to exercise or the upright posture (Prichard, 1970; Zacharias, 1971). The precise manner in which propranolol reduces blood pressure in hypertension
is uncertain. Its spectrum of activity includes blockade of the $\beta_1$-adrenoceptors of the heart, and extends to the $\beta_2$-receptors which mediate smooth muscle relaxation in bronchi, the coronary circulation, and the peripheral circulation (Barrett, 1971). From acute studies with propranolol, an antihypertensive effect of chronic oral dosage might not be anticipated. The immediate haemodynamic response to intravenous administration of propranolol is a fall in cardiac output, a rise in total peripheral vascular resistance, and no appreciable change in blood pressure (Ulrych et al., 1968). With long-term oral dosage there is a reduction in arterial pressure, heart rate, and cardiac output, and a rise in total peripheral resistance (Frohlich et al., 1968). Other effects of long-term oral dosage include reductions in plasma volume (Tarazi et al., 1971) and plasma renin activity (Michelakis and McAllister, 1972).

It has variously been suggested that the BP-lowering effect of propranolol may be related to the reduction in cardiac output, to the lower plasma renin activity, or to central effects on noradrenergic neurones (Frohlich et al., 1970; Nayler, 1972). Although cardiac output and PRA are lowered by propranolol, it remains unproven that either is a major BP-lowering mechanism. A recent finding by Tarazi and Dustan (1972), in a group of 52 hypertensives treated with propranolol, was that the fall in BP was unrelated to the degree of reduction in cardiac output. The majority of these patients had cardiac output reduced by the drug, but in most this fall in cardiac output was offset in part by a rise in total peripheral resistance. TPR rose in the group as a whole, but to a differing extent in individual
patients. The patients with the best response in blood pressure were those with the smallest rises in TPR.

Essential hypertensives differ widely in their sensitivity to propranolol, dose requirements ranging from perhaps 0.1 g to 3.0 g daily (Prichard, 1970; Zacharias, 1971). Attempts to predict the BP-lowering effect of propranolol in individual hypertensive patients have, on the whole, not been successful. An exception is in essential hypertensives with "hyperdynamic β-adrenergic disease" (Fröhlich et al., 1969), in whom a raised blood pressure is associated with cardiac symptoms, such as palpitations, and excessive sensitivity to infused β-agonist can be demonstrated. Both cardiac symptoms and elevated BP respond to a relatively low dose of propranolol in these patients. Initial impressions (Fröhlich et al., 1970) that among essential hypertensives, those with an elevated cardiac output are most sensitive to the BP-lowering effect of propranolol, have not been confirmed (Tarazi and Dustan, 1972).

The antihypertensive activity of some other β-adrenoceptor blockers has been evaluated. Practolol (Prichard et al., 1971), oxprenolol (Waal-Manning, 1970) and prindolol (Waal-Manning, 1970) have all been shown to lower arterial pressure in essential hypertension. The antihypertensive activity of these agents relative to that of propranolol is uncertain. In the only comparative trial, (Waal-Manning, 1970), propranolol, practolol, oxprenolol, and prindolol were found to be of similar potency, but in this trial a 2-week crossover design was used, and a residual effect on blood pressure from the previous
ß-adrenergic blocker may well have been present when a particular drug was being evaluated.

Practolol differs from propranolol in its spectrum of action. Its ß-adrenoceptor blocking activity is confined largely to ß₁-receptors, so that it is relatively cardioselective (Barrett, 1971). It has predominantly a negative chronotropic effect on the heart, with a minimal negative inotropic effect (Finegan et al., 1972). Blocking activity for ß₂-receptors, which mediate smooth muscle relaxation in the bronchi, coronary vessels, and peripheral vascular tree, is much less than that of propranolol (Barrett, 1971). The reduction in BP produced by propranolol is closely and inversely related to change in total peripheral resistance. BP falls are larger in patients with little or no rise in TPR (Tarazi and Dustan, 1972). The basis of the rise in TPR is not completely understood. It may be reflex, and related to the reduction in cardiac output, or perhaps reflects peripheral vascular ß₂-adrenoceptor blockade. As practolol has little ß₂-adrenoceptor blocking activity and changes in TPR with long-term oral dosage are minimal (Bodem et al., 1971), the antihypertensive activity of practolol might be anticipated to be at least equal to that of propranolol.

Propranolol in low dosage has been used to control the elevation of blood pressure in hypertensives with "hyperdynamic ß-adrenergic disease", in whom it has been suggested there is increased sensitivity of ß-adrenoceptors to catecholamines (Frohlich et al., 1969). It seemed possible that differences in the individual sensitivity of hypertensive patients to the BP-lowering
effects of β-adrenergic blocking drugs might be related to differences in reflex activity of the sympathetic nervous system. This possibility has been investigated in a drug trial in which practolol was used as the sole antihypertensive agent, and the relationship between fall in blood pressure on the drug, and reflex sympathetic response to tilting prior to commencing treatment, has been assessed (Chapter 5).
CHAPTER 2

METHODS

The experimental designs of individual studies are described in subsequent Chapters. In this Chapter, general aspects of methodology are considered.

ESTIMATION OF SYMPATHETIC NERVOUS ACTIVITY

The events following sympathetic nerve stimulation have been reviewed by Andén et al. (1969). Stimulation of adrenergic nerves causes quantal release of noradrenaline, accompanied by proportional amounts of other granular components, such as adenine nucleotides and the enzyme dopamine β-hydroxylase. The released noradrenaline produces post-synaptic excitation, and is "inactivated" by several different mechanisms, including reuptake by the membrane pump, diffusion into the blood, and to some extent local enzymatic destruction by catechol-O-methyltransferase (COMT). Plasma levels of noradrenaline are determined by the amount of transmitter released, the activity of the local mechanisms of neuronal reuptake and enzymatic degradation by COMT, the rate of diffusion into the blood, and the rate of extraction of noradrenaline from plasma. The degree to which the plasma noradrenaline level reflects the rate of noradrenaline release depends on the circumstances. If the inactivating mechanisms are impaired, such as by blocking the neuronal pump, diffusion of noradrenaline into the blood will be enhanced, and plasma levels of the amine will more closely reflect the rate of noradrenaline release. Under conditions of increased blood flow, such as during hard muscular exercise, diffusion
of noradrenaline into the blood is increased, and the plasma noradrenaline more faithfully reflects the rate of noradrenaline release (Andén et al., 1969).

Under less ideal conditions, this relationship no doubt holds less closely, but there is good evidence that the plasma (and urinary) level of noradrenaline is a qualitatively valid if quantitatively inexact index of sympathetic nervous activity. Patients with autonomic degeneration excrete reduced amounts of noradrenaline in the urine (Goodall et al., 1968). When a sympathetic nerve trunk is electrically stimulated the rate of noradrenaline release into venous blood is directly related to the frequency of nerve discharge (Brown and Gillespie, 1957). Plasma and urinary noradrenaline levels rise in response to head-up tilting, and the magnitude of the response is directly related to the angle of tilting (Sundin, 1956; Hickler et al., 1959). It would seem that the change in noradrenaline level is at least a valid semi-quantitative index of change in sympathetic nervous activity.

One problem is that the relative contribution by sympathetic nerves from different sites to the total noradrenaline plasma pool cannot be determined. This applies to head-up tilting, which has been used as an adrenergic stimulus in this work. Since adrenalectomized patients have been shown to have a normal noradrenaline response to tilt (von Euler and Franksson, 1957) it is presumed that the sympathetic nerves to arterioles are the major source of the noradrenaline increment. But other sites, such as the heart (Braunwald et al., 1964) may also contribute.
Plasma Catecholamine Assays

Because of very high blank fluorescence, assay systems for plasma catecholamines have been characterized by poor reproducibility. A recently described modification of the trihydroxyindole method, in which a concentrating step on an ion exchange resin has been introduced, seems to have overcome the problem of high background fluorescence (Valori et al., 1970). The double-isotope derivative assay of Engelman and Portnoy (1970) is also a sensitive and accurate technique.

Free Urinary Catecholamines

To what extent urinary catecholamine excretion in man reflects plasma levels remains an open question. In this work, urinary noradrenaline and adrenaline excretion and endogenous creatinine clearance have been measured concurrently, and adjustment made for within-group differences in GFR, and for incomplete emptying of the bladder, as follows:

Adjusted catecholamine excretion (μg catecholamine/litre of plasma cleared of creatinine) = catecholamine excretion (μg/min)/GFR(litre/min). As with the commonly adopted convention of expressing urinary catecholamines simply in relation to the rate of excretion of creatinine, the assumption is made that adrenaline and noradrenaline excretion is a function only of plasma levels and glomerular filtration, renal tubular mechanisms having no role. This remains unproven in man, and the evidence from animal experimentation is conflicting (Rennick and Pryor, 1965; Overy et al., 1967). Formal clearance studies in man are
needed to clarify this point, but until definitive information is available, the adjustment of catecholamine excretion rates for differences in GFR would seem a satisfactory compromise. In 32 normal subjects with a wide range of creatinine clearances, a close correlation was observed between creatinine clearance and urinary noradrenaline excretion; \( r = 0.67, p < 0.001, \) Fig. 2-1. Adjusted adrenaline and noradrenaline levels (\( \mu g \) catecholamine excreted per litre of plasma cleared of creatinine) in normal subjects and in patients with essential hypertension (Chapter 7) proved to be very similar to published plasma levels measured by a double-isotope derivative assay (Engelman and Portnoy, 1970; De Quattro, 1972).

Total Urinary Catecholamines, Vanillyl Mandelic Acid, Normetadrenaline

For most purposes, the estimation or urinary free catecholamines is preferable to measuring total urinary catecholamines (free plus conjugated) (Crout, 1961). Urinary excretion of the acid-labile conjugates may be influenced by diet (Crout and Sjoerdmsma, 1959), contributes up to 60% of the total urinary noradrenaline excretion (Elmadjian et al., 1956), and gives little indication of the level of free noradrenaline in plasma. Urinary vanillyl mandelic acid (VMA) excretion has been used as an index of sympathetic nervous activity, and urinary VMA and total free catecholamine excretion correlate significantly (Nestel and Doyle, 1968). But VMA is partly derived from adrenaline, and from deamination of "firmly bound" noradrenaline in the nerve ending (Kopin, 1964), so it would
be anticipated that excretion of VMA would be a less sensitive index of sympathetic nervous activity than noradrenaline excretion. There is evidence that released noradrenaline that diffuses from receptors is preferentially metabolized by O-methylation (Hertting and Axelrod, 1961). It is uncertain whether in man urinary normetadrenaline provides a better index of sympathetic activity than urinary noradrenaline (De Quattro and Sjoerdsma, 1968).

**Isotopic Studies**

Techniques have been devised for measuring the turnover rate of isotopically-labelled noradrenaline, and from comparison of the half-times, the relative activity of the sympathetic nervous system has been inferred. Studies in which labelled noradrenaline is administered (Gitlow *et al.*, 1964) have been difficult to interpret because these have not used "tracer" doses, and provide information only about noradrenaline clearance from plasma. If labelled noradrenaline precursors are administered, turnover rates of C\(^{14}\) noradrenaline will provide a measure of noradrenaline synthesis and metabolism, to the extent that the precursors mix homogeneously with the various neuronal noradrenaline pools (De Quattro and Sjoerdsma, 1968). A further problem in interpretation is that turnover rates will be influenced by intra-neuronal deamination, in addition to the rate of noradrenaline release and O-methylation.

**Dopamine-β-hydroxylase**

Noradrenaline and the enzyme dopamine-β-hydroxylase (DBH) are discharged in proportional amounts, by a process
of exocytosis, on stimulation of adrenergic nerves (Axelrod, 1972). A sensitive assay for DBH has been developed (Molinoff et al., 1971) and it is now possible to measure DBH activity in the plasma of man (Weinshilboum and Axelrod, 1971). The serum DBH arises from sympathetic nerve terminals and not from the adrenal medulla (Axelrod, 1972). As DBH, unlike noradrenaline, is not subjected to reuptake after release, serum DBH levels hold promise of being a sensitive biochemical index of sympathetic nervous activity.

Studies of sympathetic nervous system activity and responsiveness in man have been plagued by the lack of a totally reliable, quantifiable chemical marker of postsynaptic sympathetic nerve fibre discharge. It is doubtful that the excretion of a single substance, be it noradrenaline, normetadrenaline, or VMA, provides a strictly quantitative chemical index of sympathetic activity. But for reasons presented, it would seem that the change in noradrenaline level with adrenergic stimulation provides at least a semi-quantitative index of change in sympathetic nervous activity. At the time of commencement of this work, existing plasma catecholamine assays were of doubtful reproducibility, and the decision was made to measure urinary free adrenaline and noradrenaline levels, by Crout's modification (Crout, 1961) of the trihydroxyindole method (Lund, 1949). From evidence presented here, and in Chapter 7, there is reason to believe that urinary catecholamine levels, adjusted for within-group differences in GFR, closely reflect plasma catecholamine levels. The recently introduced fluorimetric (Valori et al., 1970) and
double-isotope derivative (Engelman and Portnoy, 1970) assays for plasma catecholamines have the advantage of allowing the time course of an adrenergic response to be studied more closely. The serum dopamine-β-hydroxylase assay (Molinoff et al., 1971) holds promise of providing at last a method for accurate biochemical quantitation of sympathetic nervous system responses.

ASSAY OF URINARY FREE CATECHOLAMINES

Urinary free adrenaline and noradrenaline were estimated using Crout's modification (Crout, 1961) of the trihydroxyindole method (Lund, 1949), with differential fluorimetry using 2 sets of filters (von Euler and Lishajko, 1959). The trihydroxyindole assay is a 3-stage procedure:

1. The catecholamines are isolated from urine and concentrated into a relatively pure extract by adsorption on alumina.

2. Noradrenaline and adrenaline are oxidized to aminochromes, then converted to fluorescent indole derivatives in alkaline solution.

3. The amines are measured fluorimetrically.

In the method of Crout, the catecholamines are isolated from urine by a batch extraction with alumina, and eluted from the alumina with 0.20 N acetic acid. The oxidant used was 0.25% potassium ferricyanide (von Euler and Lishajko, 1959), not the 0.1 N iodine solution used by Crout. Interference from dopamine is less when ferricyanide is used (von Euler and Floding, 1956). The problem of quenching was overcome by the use of EDTA, which prevents the formation of a gelatinous calcium magnesium phosphate
precipitate in the final reaction mixture, and by running an internal catecholamine standard through the entire procedure.

Adrenaline and noradrenaline were assayed separately by differential fluorimetry using 2 pairs of settings for excitant and emergent wavelength (von Euler and Lishajko, 1959). A Turner III fluorimeter and the following 2 filter systems were used:

**Setting a**
- Excitant: Wratten Filter (110-812), approx. 405 μm.
- Emergent: Wratten Filter (65A), approx. 495 μm.
This setting reads fluorescence for adrenaline: noradrenaline = 1:1.

**Setting b**
- Excitant: Wratten Filter (2A+47B), approx. 436 μm.
- Emergent: Wratten Filter (2A-15), approx. 520 μm.
Setting b reads adrenaline:noradrenaline = 3:1.

The adrenaline and noradrenaline content of the sample was derived from the simultaneous equations:

Noradrenaline = \( y = \frac{A^b_a}{A^a_a} - \frac{n}{N^a_a} (\frac{A^b_a}{A^a_a} - N^b_b) \)

Adrenaline = \( x = n - yN^b_b/A^b_b \)

\( m = \) Sample fluorescence-Blank fluorescence on filter setting a.

\( n = \) Sample fluorescence-Blank fluorescence on filter setting b.

\( A^a_a, A^b_b = \) Fluorescence of adrenaline external standard on settings a and b.
\[ N_a, N_b = \text{Fluorescence of noradrenaline external standard on settings a and b.} \]

Recovery of added noradrenaline was \(76 \pm 6\%\) (mean \pm standard deviation of difference in assayed duplicate pairs), and for added adrenaline was \(75 \pm 10\%\). Urinary catecholamine estimates were adjusted for recovery, based on the recovery of the internal standards in the day's assay.

**ASSAY OF PLASMA RENIN ACTIVITY**

Plasma renin activity was estimated by the bioassay method of Skinner (1967), using the anaesthetized ganglion-blocked rat. Recovery of angiotensin II added prior to preparation of the plasma was \(82 \pm 7\%\) (mean \pm standard deviation). The assay recorded zero plasma renin activity, at 60 hours incubation, in blood from a nephrectomized patient. The difference between 24 duplicate measurements of PRA was \(6 \pm 9\%\) (mean \pm standard deviation). The assay was performed in duplicate, on 2 different rats, and was repeated if duplicates differed by more than \(24\%\) (mean difference \(+ 2.5\text{S.D.}\)).

**ENDOGENOUS CREATININE CLEARANCE**

Urinary creatinine was determined by a modification of the alkaline picrate method (Edwards and Whyte, 1958). Each estimation was performed in duplicate. Coefficient of variation for the assay, standard deviation \(\times 100/\text{mean},\) was 3%. Serum creatinine was measured by an SMA autoanalyzer.

There is considerable disagreement over the relationship of endogenous creatinine clearance to inulin clearance in health and in renal disease (Healy, 1968). Disparity is
thought to arise from renal tubular secretion of creatinine (Shannon, 1935), and from the presence of non-creatinine chromogen in plasma. Creatinine clearances based on plasma creatinine measurement using an autoanalyzer tend to give an underestimate of GFR when GFR is in the normal range, and to overestimate GFR when it is reduced. In a study by Healy (1968), in which inulin clearance and autoanalyzer endogenous creatinine clearance were simultaneously determined in 30 subjects, there was a correlation coefficient of 0.86 between results from the 2 methods. In the 10 subjects with GFR greater than 90 mls/min, the ratio of autoanalyzer creatinine clearance to inulin clearance was 0.91.

In the studies to be described in subsequent Chapters, the estimation of GFR has been based on autoanalyzer creatinine clearances. In most cases, an estimate only of change in GFR was required, not of the absolute value. In Chapter 7, where urinary catecholamine excretion is adjusted for within-group differences in GFR (estimated from autoanalyzer creatinine clearance), although absolute values are subject to a systematic error of approximately 10%, the comparison of catecholamine levels in the different patient groups studied remains valid.

PSYCHOLOGICAL TESTING

The psychometric testing of hypertensive subjects employed questionnaire techniques. Questionnaires used were the I.P.A.T. Anxiety Scale Questionnaire (Cattell and Scheier, 1963), and the Eysenck Personality Inventory, Form A (Eysenck and Eysenck, 1964) which measures
2 dimensions of personality, neuroticism-stability, and extraversion-introversion. The I.P.A.T. Anxiety Scale gives a measure of free-floating, manifest anxiety, which is increased in situationally determined anxiety reactions, or in chronic anxiety neurosis relatively independent of the immediate situation (Cattell and Scheier, 1963). Neuroticism, as measured by the Eysenck Personality Inventory, describes quantitatively the spectrum of personality ranging from stable individuals (low neuroticism score) through to unstable "neurotic" individuals (high neuroticism score).

For comparative purposes, a general medical group of 40 patients, drawn from a medical ward and its associated outpatient department, and constituting a consecutive series of all new referrals in the age range 20-60 years, was studied. None of these patients was acutely ill at the time of testing, and most had been referred for diagnostic procedures.

EXPERIMENTAL SUBJECTS
Essential Hypertensives

Patients with essential hypertension were drawn from more than 100 patients referred, during a 3-year period, for investigation of an elevated blood pressure. Secondary hypertension was reasonably excluded by routine screening procedures including urine microscopy and culture, serum sodium and potassium levels, endogenous creatinine clearance, urinary catecholamine excretion, and in most cases intravenous pyelography (no intravenous pyelogram in 7 patients with borderline hypertension). None of the
female patients was taking oral contraceptive drugs. Most patients studied had never received treatment for the hypertension. A minority had received some treatment in the past, though not in the preceding 12 months.

Subjects with Normal Blood Pressure

The normotensive subjects consisted of student volunteers, and ambulant general medical patients drawn from a medical ward and its associated outpatient department. None of the patients was acutely ill, and most had been referred for diagnostic procedures.

The experimental procedures were explained fully to the subjects, and signed consent was obtained from all normal volunteers.

MISCELLANEOUS

(a) Urinary sodium and potassium were estimated with an EEL flame photometer.

(b) Plasma volume was measured using Evans Blue (Lawson, 1962). Blood volume was calculated from estimates of plasma volume and mean haematocrit (Chaplin et al., 1953).

(c) Blood pressure was measured with a sphygmomanometer, bag dimensions 30 x 12.5 cm, with the cuff at heart level.

(d) The "Severity Index" of the hypertensive disease was calculated using the point-score system of Corcoran et al. (1954).

(e) Excess body weight was expressed as a ponderal index (Grace and Goldrick, 1969).

(f) Statistical analyses were performed according to Snedecor (1956).
Figure 2-1. The relationship between creatinine clearance and urinary noradrenaline excretion in subjects with a normal blood pressure; $r = 0.67$, $p < 0.001$. 
The effect of 25° head-up tilt on blood pressure, urinary catecholamines, and creatinine clearance has been studied in untreated essential hypertensive patients and normotensive subjects.

The mean rise in diastolic pressure for all hypertensives was 4.9 mmHg which did not differ significantly from the mean rise of 5.4 mmHg in the normal subjects. Ten of 41 hypertensives had a diastolic pressure response greater than the response in any of 11 normal subjects, with a rise of greater than 10 mmHg.

The increase in urinary noradrenaline excretion with tilt was greater in these orthostatic hypertensives (1.74 \( \mu \)g/hr) than in either the remaining hypertensives (0.34 \( \mu \)g/hr) or the normotensive subjects (0.56 \( \mu \)g/hr). Overall there was a significant correlation between changes in diastolic blood pressure and urinary noradrenaline.

Creatinine clearance was reduced by tilting. The mean reduction was similar for normally reacting hypertensive and normotensive subjects (6% and 7.2% respectively). The 10 orthostatic hypertensives, however, had a greater reduction in creatinine clearance (23.4%), and in the hypertensive group as a whole, change in diastolic blood pressure and creatinine clearance were negatively correlated.

The tilt hyperresponders tended to be young, not obese, and with recent onset of hypertension when documentation of this was adequate.
INTRODUCTION

In spite of the efficacy of adrenergic blocking drugs in lowering blood pressure in essential hypertension, it is generally thought that the unstimulated activity of the sympathetic nervous system and adrenal medulla is normal in this disorder (Peart, 1966). This apparent paradox has led to studies on responsiveness to stimuli that activate the sympatho-adrenomedullary system. Such stimuli include change in posture, which activates the sympathetic nervous system primarily, stimulating noradrenaline secretion (Sundin, 1956) and initiating neurovascular reflexes that affect blood pressure and modify renal function (Lee et al., 1966). In one such study (Fröhlich et al., 1967), a proportion of hypertensive subjects responded abnormally to the stimulus of head-up tilt, with enhanced increases in blood pressure and total peripheral vascular resistance. We have investigated the question of sympathetic responsiveness further, by measuring responses in blood pressure, urinary noradrenaline and glomerular filtration rate to head-up tilting in a group of normotensive and untreated essential hypertensive subjects.

METHODS

Forty-one untreated white hypertensive patients (30 sustained essential hypertension, 11 borderline hypertension) and 11 white normotensive subjects were studied. Of the hypertensives, 32 had received no previous treatment for the hypertension, while 9 had received treatment for the hypertension in the past, but not in the preceding 12 months. The absence of recent treatment was related to the fact that all were either newly diagnosed hypertensives, borderline
hypertensives, or previously diagnosed defaulters who had recently renewed contact with doctors, and were now referred for diagnostic procedures. The blood pressure elevation was designated sustained hypertension or borderline hypertension on the basis of average casual, or "usual", blood pressure (Julius and Schork, 1971). The average blood pressure during the first 2 days of hospital admission, or over several outpatient attendances, was in excess of 155/95 mmHg in each of the patients with sustained hypertension. In patients with borderline hypertension, the average pressure under these conditions in each case fell within the range 145/90 - 155/95 mmHg, although occasional values were sometimes above 155/95 mmHg and sometimes below 145/90. The figures of 155/95 and 145/90 are based on the distribution of blood pressure in population studies, such as reviewed by Julius and Schork (1971). Subjects with isolated systolic hypertension and normal diastolic pressures were not included in the study. Secondary hypertension was reasonably excluded by routine screening procedures including urine microscopy and culture, serum and 24-hour urinary sodium and potassium levels, endogenous creatinine clearance, urinary catecholamine excretion, and in most cases intravenous pyelography (no intravenous pyelogram in 4 patients with borderline hypertension). None of the female hypertensives was taking oral contraceptive drugs. The severity of the hypertensive disease was graded according to the scale of Corcoran et al. (1954), and the patients' adiposity estimated from a ponderal index (Grace and Goldrick, 1969). In 26 of the 41 hypertensive patients it was felt that
estimation of the duration of hypertension was possible, with adequate documentation from previous frequent medical examination related primarily to employment. Duration was dated from the time that elevated pressure was first noted, whether borderline or sustained elevation. The 11 normotensive subjects comprised 7 student volunteers and 4 ambulant hospital inpatients. None had cardiovascular disease, or a family history of hypertension.

The investigation was performed on the hypertensives as outpatients (23 subjects) or during the first two days of hospital admission (18 subjects) to minimize any effects of confinement and prolonged recumbency (Dietrick et al., 1948). Changes with tilting in blood pressure, urinary noradrenaline, and glomerular filtration rate were measured. After an overnight fast, subjects were rested supine in a single bed ward for 90 minutes prior to the commencement of the study. Then followed a 90-minute period of recumbent rest, and after venepuncture, a further 90 minutes consisting of 15 minutes for stabilization of blood pressure and pulse rate after venepuncture, and terminating in 75 minutes of head-up tilt. Subjects voided at the end of both these periods, and the urine was acidified and frozen for storage prior to estimation of catecholamines and creatinine. Drinking water was given throughout to ensure an adequate urine flow. Blood pressure was measured with a sphygmomanometer at 10-minute intervals during the period of recumbent rest. Disappearance of sound was taken as the diastolic end-point. Blood was drawn at the end of the period of recumbency for estimation of serum creatinine. After collection of the first urine sample and venepuncture,
blood pressure and pulse rate were repeatedly measured until they had returned to pre-venepuncture levels, which invariably occurred within 15 minutes. A stable pre-tilt baseline having been obtained, subjects were then tilted head-up on a tilt-table with a boot-board at 25° tilt for 75 minutes. With the sphygmomanometer cuff at heart-level, blood pressure was measured at 2-minute intervals for the first 20 minutes of tilt and at 10-minute intervals thereafter. Blood pressure and pulse rate changed on tilting to reach a stable peak response within 5 minutes or so, then remained almost constant for 20-30 minutes, after which there was a gradual return towards pre-tilt values. The blood pressure and pulse rate responses were taken as the means of the 3 maximum deviations from the immediate pre-tilt levels during the first 20 minutes of tilt. This in effect recorded the plateau of blood pressure and pulse rate response to tilt, eliminating the periods of early circulatory adjustment, and slow return towards baseline if this occurred sooner than 20 minutes after commencing tilt.

Urinary free noradrenaline and adrenaline were determined in duplicate with a Turner III fluorimeter by differential fluorimetry with 2 sets of filters (von Euler and Lishajko, 1959) but otherwise using the method of Crout (1961). Internal standards were carried through the entire procedure.

Urinary creatinine was determined by the alkaline picrate method (Edwards and Whyte, 1958) and serum creatinine by autoanalyzer.
In 18 subjects, plasma volume was measured on the morning of the test using Evans Blue. From this, and the estimated mean haematocrit (Chaplin et al., 1953), blood volume was calculated.

Questionnaire-based psychometric testing was performed in patients with elevated blood pressure. Psychometric testing was performed within 2 weeks of the tilt studies, but not on the day of the tilt test. Questionnaires used were the I.P.A.T. Anxiety Scale Questionnaire (Cattell and Scheier, 1963) which is primarily a measure of free-floating or manifest anxiety, and the Eysenck Personality Inventory (Eysenck and Eysenck, 1964) which measures 2 dimensions of personality, neuroticism-stability and extraversion-introversion.

RESULTS

The relevant details about the subjects, and the responses to tilt, are listed in Tables 3-1, 3-2, and 3-3.

For the purposes of this study, patients with borderline and sustained hypertension have been incorporated into a single group. They have been treated as a continuum in this way to facilitate evaluation of the responses in relation to the severity index of the hypertensive process. This is not to imply homogeneity of the group, or a necessary progression with time from borderline to sustained hypertension. Although some indices of sympathetic responsiveness correlated overall with severity of the hypertension, in no case did the response in borderline hypertensives as a group differ significantly from that in sustained hypertensive or normotensive subjects.
Change in Systolic Blood Pressure

The change in systolic blood pressure in the hypertensives was $-4.5 \pm 7.8$ mmHg (mean ± standard deviation) and in the normotensives $-1.1 \pm 4.0$ mmHg. The difference in the means was not significant, but the hypertensives demonstrated a significantly greater scatter of systolic pressure responses (variance ratio = 3.80, $p < 0.01$). The normal subjects maintained their systolic blood pressure in the face of orthostatic stress better than many of the hypertensives, 13 of whom, with falls of 10 mmHg or more, had a fall in systolic blood pressure more than 2 standard deviations greater than the mean fall in the normal subjects. These hypertensives tended to have more severe disease and overall there was a significant negative correlation between changes in systolic blood pressure and severity index ($r = -0.37$, $p < 0.02$).

Change in Diastolic Blood Pressure

Change in diastolic blood pressure in the hypertensives was $+4.9 \pm 6.6$ mmHg and in the normotensives, $+5.3 \pm 3.3$ mmHg (difference in means not significant; variance ratio = 3.76, $p < 0.01$). Ten of 41 hypertensives, with diastolic blood pressure rises of 11 mmHg or more, reacted as "orthostatic hypertensives" with a rise in diastolic pressure greater than the rise in any of 11 normal subjects. Of the 10 orthostatic hypertensives, 4 had borderline hypertension, 4 had mild sustained hypertension and 2 (patients 7 and 9) had moderately severe sustained hypertension. For the hypertensive group as a whole there was only a low order of negative correlation between changes in diastolic blood pressure and severity index ($r = -0.27, 0.05 < p < 0.1$).
Change in Urinary Noradrenaline

There were substantial changes in creatinine clearance with tilting, and urinary noradrenaline excretion was corrected for these changes*. There was a significant rise in uncorrected mean urinary noradrenaline excretion, +0.41 μg/hr for hypertensives (p < 0.01, paired t-test) and +0.42 μg/hr for normotensives (p < 0.05). The changes in adjusted urinary noradrenaline excretion, +0.68 ± 0.96 μg/hr for hypertensives and +0.56 ± 0.51 μg/hr for normotensives, did not differ significantly, but hypertensives demonstrated a wider range of noradrenaline responses (variance ratio 3.54, p < 0.02). In 8 of 41 hypertensives, who showed increases greater than 1.6 μg/hr the noradrenaline response was more than 2 standard deviations beyond the mean increment for normal subjects. Of these 8 noradrenaline hyperresponders, 6 behaved also as orthostatic hypertensives.

For the hypertensive group as a whole there was a significant correlation between changes in diastolic blood pressure and urinary noradrenaline (r = 0.53, p < 0.001) (Fig. 3-1).

The noradrenaline response tended to be smaller in patients with longstanding hypertension (duration of hypertension vs. noradrenaline response, r = -0.38, 0.05 < p < 0.1: (Fig. 3-2)).

* Change in noradrenaline = measured urinary noradrenaline (tilted) x creatinine clearance recumbent/creatinine clearance tilted - measured urinary noradrenaline (recumbent).
There was also a trend for severity index and noradrenaline responsiveness to be negatively correlated, although this did not reach statistical significance (Fig. 3-3).

There was no correlation between the level of urinary noradrenaline during recumbency and the increase with tilting.

Blood volume was measured in 10 male hypertensives and 8 male normotensives. Noradrenaline response to tilt was unrelated to blood volume in either group.

Change in Creatinine Clearance

A fall in mean creatinine clearance occurred with tilt, and this was of similar magnitude in hypertensives and normotensives with reductions of 10.2 ± 17.2% and 7.2 ± 13.7% respectively. The large standard deviations partly reflect technical factors as endogenous creatinine clearances based on voided specimens give less than ideal reproducibility. Coefficient of variation* for endogenous creatinine clearance performed at the same time on successive days in 20 subjects was 11.9% and coefficient of variation for successive collection periods on the same day has been reported as 8.1% (Healy, 1968). But the scatter of responses observed probably also reflects physiological differences. The mean fall in the orthostatic hypertensives was 21.3% compared with a fall in the remaining hypertensives of 6.0% (t = 2.92 p < 0.01),

* Coefficient of variation = 100 x \( \frac{\sqrt{\text{Error variance}}}{\text{Combined mean}} \)
and for the hypertensive group as a whole, there was a significant correlation between rise in diastolic blood pressure and fall in creatinine clearance; \( r = 0.40, p < 0.01 \) (Fig. 3-4).

**Psychometrics**

Anxiety scores in borderline hypertensives, 23.2 ± 10.5, and sustained hypertensives, 30.7 ± 13.4, did not differ significantly. The neuroticism scores in borderline and sustained hypertension, 7.9 ± 5.5 and 10.9 ± 5.8 respectively, also were not significantly different. Overall, there was no correlation between anxiety and neuroticism scores, and the sympathetic responses to tilting shown by the hypertensives.

**DISCUSSION**

An accentuated blood pressure rise with tilting occurs in approximately one third of all patients with essential hypertension (Frohlich et al., 1967). Results have been presented here consistent with the concept that enhanced sympathetic nervous system responsiveness underlies an orthostatic hypertensive response. This enhanced responsiveness was manifested as greater change in diastolic blood pressure, urinary noradrenaline, and glomerular filtration rate in the hyperresponders to tilt.

The basis of such an enhanced responsiveness remains uncertain, but it seems unlikely that the tilt hyperresponders were more anxious than the remaining hypertensives, and that an accentuated response to tilting only reflected a greater degree of apprehension about the procedure. Questionnaire scores of anxiety and neuroticism in the tilt hyperresponders
did not differ significantly from the scores in the remaining hypertensives. Furthermore, adrenaline excretion, an index of anxiety (von Euler, 1964), was not raised in the orthostatic hyperresponders.

Some of the clinical characteristics of the tilt hyperresponders, the 12 hypertensives with greater rises in diastolic blood pressure, urinary noradrenaline, or both, than seen in normotensives, warrant mention. As a group, the tilt hyperresponders tended to be young, not obese, with hypertension of recent onset. All 12 hyperresponders were less than 45 years while 10 of 29 normal responders were over 45 (p < 0.05*). Age appears to have little influence on noradrenaline, blood pressure or renal responses to orthostatic stress in normal subjects (Lee et al., 1966; Hickler et al., 1959; Strandell, 1964). Duration of the hypertension was known in 8 of the 12 tilt hyperresponders, and was in no case more than 5 years. In 9 of 18 normally responding patients, hypertension had been present for more than 5 years (p < 0.05*) and in 7 for 10 years or more. Fourteen of 29 normally responding hypertensives were obese, having a ponderal index of 2.6 or more, equivalent to greater than 115% ideal body weight. None of the 12 hyperresponders were obese (p < 0.01*). An enhanced sympathetic responsiveness to tilt may be a common accompaniment of early, mild essential hypertension, to be lost later if the hypertensive process becomes more severe. It is of interest in this regard that when the study was repeated after an interval of 1-2 years, in 4 patients with mild sustained hypertension, and one with borderline hypertension, who initially showed an

* Chi-square test of significance
accentuated response to tilting, the changes in diastolic blood pressure, urinary noradrenaline, and creatinine clearance observed on retesting were marginally lower than the earlier responses in each of these 5 patients. However the responses were not significantly less (paired t-test), and in 4 of the 5 still constituted a greater than normal response to tilt.

The evidence for increased sympathetic activity in essential hypertension has been reviewed by Nestel and Esler (1970). It seems probable that resting hypertensive subjects on the whole do not excrete increased amounts of catecholamines, although a proportion of hypertensives demonstrate elevated excretion of catecholamines and their metabolites. In the present study, 8 of 41 hypertensive patients had a resting urinary excretion of noradrenaline more than 2 standard deviations greater than the mean excretion rate in the normal subjects. These tended to be patients with higher blood pressures and more severe hypertensive disease. Among subjects with mild, untreated hypertension the output of catecholamines may be normal in the absence of stress, but may be above normal during stress. An increased response measured in terms of increased arterial pressure and urinary catecholamines, has also been observed in young, mild hypertensive patients when stressed with mental arithmetic (Nestel, 1969).

There are several studies in the literature reporting normal plasma and urinary noradrenaline responses to tilt in essential hypertension (Sundin, 1956; Hickler et al., 1959). These differ from the present study in several respects. The number of patients studied was generally
small, and included mainly those with severe sustained hypertension. An enhanced noradrenaline response to change in posture has been described in subjects with "hyperkinetic circulation", in association with both normal and elevated blood pressure (Kuchel et al., 1970). It is of interest in this regard that 3 of the tilt hyperresponders had symptoms of recurrent palpitations and chest discomfort suggestive of hyperdynamic β-adrenergic disease (Fröhlich et al., 1969).

Differences in blood pressure responses to tilt between normally reacting hypertensives and orthostatic hypertensives reflect a greater increase in total peripheral vascular resistance in the latter (Fröhlich et al., 1967). In this study, orthostatic hypertensives had the largest increment in urinary noradrenaline, and for all hypertensives, a significant relationship was found between the increments in diastolic pressure and urinary noradrenaline. This suggests a possible quantitative relationship between increased sympathetic nerve discharge to arterioles and the rise in diastolic pressure. Although the rate of noradrenaline excretion in the urine is a very indirect measure of sympathetic activity, several lines of evidence suggest that it may be a valid index. Patients with autonomic degeneration excrete reduced amounts of noradrenaline in the urine (Goodall et al., 1968). When a sympathetic nerve trunk is electrically stimulated the rate of noradrenaline release into venous blood is related to the frequency of sympathetic nervous discharge (Brown and Gillespie, 1957). Plasma and urinary noradrenaline concentrations rise in response to change in posture (Sundin, 1956; Hickler et al., 1959) but the relative contribution
by sympathetic nerves in different sites to the total noradrenaline plasma pool is unknown. Since adrenalectomized patients have been shown to have a normal noradrenaline response to tilt (von Euler & Franksson, 1957) it is presumed that the sympathetic nerves to arterioles are the major source of the noradrenaline increment. But other sites, such as the heart (Braunwald et al., 1964) may also contribute. Furthermore, an increase in the amount of noradrenaline overflowing into plasma may reflect diminished reuptake by the nerve ending, and need not necessarily indicate an increased frequency of sympathetic nerve discharge. Finally, it has been assumed that plasma noradrenaline is passively handled by the kidney, so that urinary excretion, corrected for differences in glomerular filtration rate, reflects the plasma concentration. Although this assumption is commonly made, there is no evidence available on this point in man, and some evidence to the contrary in dogs (Overy et al., 1967).

Renal physiology is affected by posture. Tilting reduces renal blood flow and glomerular filtration rate and elevates renal vascular resistance (Lee et al., 1966). It has been suggested that the fall in GFR is produced by vasoconstriction of afferent arterioles (Smith, 1939-40). We have found that the orthostatic hypertensives had the largest falls in GFR, and for the hypertensive group as a whole, change in diastolic pressure and GFR were negatively correlated. As an increase in total peripheral vascular resistance underlies the increase in diastolic pressure with tilting (Frohlich et al., 1967), increases in renal afferent arteriolar resistance and total peripheral resistance would seem to be closely related.
From which level of the barostat reflex arc the broad spectrum of responsiveness in essential hypertension derives is not clear. The response to tilt may be influenced by blood volume (Jeffrey et al., 1970; Ramirez and Abelman, 1968). Contraction of the plasma volume has been described in essential hypertension, but this is a prominent finding only in patients with more severe disease (Tarazi et al., 1968). In the present study, the largest sympathetic responses tended to occur in patients with borderline and mild sustained hypertension, and in fact noradrenaline response to tilt and blood volume appeared to be unrelated. There is some evidence that the sensitivity of the baroreceptors is reduced in severe hypertension, but is virtually normal in mild hypertension (Bristow et al., 1969). This observation may be relevant to the diminished tolerance to orthostatic stress noted in some patients with more severe hypertension, but leaves the phenomenon of tilt hyperresponsiveness unexplained. A primary defect on the efferent limb of the barostat reflex, at the level of central integration of sympathetic function, or at the nerve ending, such as has been suggested in hyperkinetic circulation (Kuchel et al., 1970) remains an untested speculation.

The pathogenic significance, if any, of the broad spectrum of sympathetic nervous system responsiveness in essential hypertension is not clear, but there may be relevance to the phenomenon of 'renin unresponsive essential hypertension'. Approximately 20% of essential hypertensives have low plasma renin activity during recumbency, and react to stimuli such as upright posture.
with smaller rises in plasma renin than normal subjects (Channick et al., 1969). There is evidence that the sympathetic nervous system plays an important role in renin release (Gordon et al., 1967). The relationship of renin responsiveness to sympathetic nervous responsiveness in essential hypertension is investigated in Chapter 4.
## Hypertensive Subjects

<table>
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<th>Sex</th>
<th>Duration of Hypertension (years)</th>
<th>Usual Blood Pressure†</th>
<th>Severity Index</th>
<th>Ponderal Index (g/cm²)</th>
<th>Personality Scores</th>
<th>Recumbent Urinary Noradrenaline (µg/hour)</th>
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Mean±S.D. 39 166/105 2.45±0.30 28.8±13.1 10.1±5.6 2.00±0.80

† Usual BP = average casual BP (Julius and Schork, 1971).
* Borderline Hypertensives
### TABLE 3-2
HYPERTENSIVE SUBJECTS - RESPONSE TO 25° HEAD-UP TILT

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<thead>
<tr>
<th>Change in Systolic BP (mmHg)</th>
<th>Change in Diastolic BP (mmHg)</th>
<th>Change in Pulse Rate</th>
<th>Change in Urinary Noradrenaline (µg/hour)</th>
<th>Change in Urinary Adrenaline (µg/hour)</th>
<th>Change in Creatinine Clearance (%)</th>
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Mean ± S.D.:
-4.5±7.8  +4.9±6.6  +9.2±7.9  +0.68±0.96  +0.20±0.47  -10.2±17.2

S.D.
### NORMOTENSIVE SUBJECTS RESPONSE TO 25° HEAD-UP TILT

<table>
<thead>
<tr>
<th>Age</th>
<th>Sex</th>
<th>Ponderal Index (g/cm²)</th>
<th>Usual Blood Pressure (mmHg)</th>
<th>Recumbent Urinary Noradrenaline (µg/hr)</th>
<th>Change in Systolic BP (mmHg)</th>
<th>Change in Diastolic BP (mmHg)</th>
<th>Change in Pulse Rate</th>
<th>Change in Urinary Noradrenaline (µg/hr)</th>
<th>Change in Urinary Adrenaline (µg/hr)</th>
<th>Change in Creatinine Clearance (%)</th>
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<tr>
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<td>1.98</td>
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</table>

Mean ± S.D.

**Normotensives**

<table>
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<tr>
<th>Age</th>
<th>Sex</th>
<th>Ponderal Index (g/cm²)</th>
<th>Usual Blood Pressure (mmHg)</th>
<th>Recumbent Urinary Noradrenaline (µg/hr)</th>
<th>Change in Systolic BP (mmHg)</th>
<th>Change in Diastolic BP (mmHg)</th>
<th>Change in Pulse Rate</th>
<th>Change in Urinary Noradrenaline (µg/hr)</th>
<th>Change in Urinary Adrenaline (µg/hr)</th>
<th>Change in Creatinine Clearance (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
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<td>2.17 ± 0.31</td>
<td>114/73</td>
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<td>-1.1 ± 4.0</td>
<td>+5.3 ± 3.3</td>
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<td>+4.9 ± 6.6</td>
<td>+9.2 ± 7.9</td>
<td>+0.68 ± 0.96</td>
<td>+0.20 ± 0.47</td>
<td>-10.2 ± 17.2</td>
</tr>
</tbody>
</table>

**Hypertensives**

### Difference in means (t-test)

|  |  |  |  |  |  |  |  |  |  |  |  |
|---|---|---|---|---|---|---|---|---|---|---|
| p < 0.001* | - | p < 0.05* | N.S. | N.S. | N.S.* | N.S.* | N.S.* | N.S.* | N.S.* | N.S.* |

### Variance ratio

|  |  |  |  |  |  |  |  |  |  |  |  |
|---|---|---|---|---|---|---|---|---|---|---|
| 0.94 | - | 1.56 | 3.80 | 3.76 | 1.58 | 1.57 | 3.54 | 1.22 |  |

* Student's t-test

† Mann-Whitney U Test (Siegel, 1956) for items with p < 0.05 for variance ratio, in which case t-test not applicable.
Figure 3-1. The relationship between responses in diastolic blood pressure and adjusted urinary noradrenaline excretion* to 25° head-up tilt. For hypertensive and normotensive subjects combined; $r = +0.50$, $p < 0.001$.

* Change in noradrenaline = measured urinary noradrenaline (tilted) $\times$ creatinine clearance (recumbent)/creatinine clearance (tilted) - measured urinary noradrenaline (recumbent).
Figure 3-2. The relationship between duration of hypertension and adjusted noradrenaline response to tilt. Means and standard errors are shown. Numbers of subjects in each interval are indicated in brackets ($r = +0.38$, $0.05 < p < 0.1$).
Figure 3-3. Change in adjusted urinary noradrenaline excretion with tilting in normal subjects (N), borderline hypertensives (B), and 3 grades of sustained essential hypertension (I = mild hypertension, severity index < 2.5; II = moderately severe hypertension, severity index 2.5 - 5.0; III = severe hypertension, severity index > 5.0). Means and standard errors are shown. Numbers of subjects in each category are indicated in brackets.
The relationship between changes in diastolic blood pressure and creatinine clearance with 25° head-up tilt. For the hypertensive subjects, $r = -0.40$, $p < 0.01$. 

Figure 3-4.
SUMMARY

The change in plasma renin activity and urinary catecholamine excretion with head-up tilting, insulin hypoglycaemia, and "mental stress" has been studied in patients with essential hypertension and subjects with a normal blood pressure. There was a significant increment in urinary adrenaline excretion with hypoglycaemia and mental stress in both groups, but changes in PRA were minimal, there being a small but significant rise in PRA with hypoglycaemia only, in the hypertensives, and with neither stimulus in the normotensive subjects. PRA and urinary noradrenaline excretion rose significantly with tilting in the hypertensive and normotensive subjects. The PRA response was greatest in hypertensives with an enhanced sympathetic responsiveness to tilting. Conversely, in low-renin essential hypertensives, the noradrenaline response was reduced. Overall, among the hypertensive subjects, the PRA and noradrenaline responses to tilt showed a positive correlation ($r = +0.69, p < 0.01$).
INTRODUCTION

The control of renin secretion appears to be achieved through 3 independent mechanisms (Davis, 1971). The "macula densa theory" views the macula densa of the distal renal tubule as a sodium sensor, receptive to changes in sodium load delivered to the distal tubule (Vander and Carlson, 1969). The "baroreceptor hypothesis" (Skinner et al., 1964) holds the glomerular afferent arteriole to be an intrarenal baroreceptor, sensitive to changes in renal arterial pressure. The third factor directly influencing renin release is the activity of the renal sympathetic nerves (Vander, 1965) and perhaps the plasma concentration of catecholamines (Otsuka et al., 1970). The predominant mechanism mediating the renin response in a particular situation depends on the circumstances. With adrenergic stimuli, such as hypoglycaemia (Otsuka et al., 1970) and change in posture (Oparil et al., 1970), the renal sympathetic nerves and circulating catecholamines seem to have the dominant role, as the renin response can be abolished by adrenergic receptor-blocking drugs (Assaykeen et al., 1970; Winer et al., 1969).

In recent years it has become clear that in approximately 20-30% of patients with essential hypertension, plasma renin activity is low at rest, and rises less than anticipated with stimuli such as sodium depletion and the
upright posture (Crane et al., 1972). Current research is largely directed towards the possibility that in "low-renin essential hypertension" a sodium-retaining hormone, other than aldosterone, may be secreted in excess by the adrenal gland (Woods et al., 1969). It is thought likely that the suppression of renin release reflects sodium retention. The activity of the sympathetic nervous system in this disorder has been little studied. Crane et al. (1972) have reported low urinary catecholamine excretion in low-renin essential hypertension, but Jose et al. (1970) found PRA and urinary catecholamine level to be unrelated. A reduction in the reflex responsiveness of the sympathetic nervous system has been described in essential hypertension (Frohlich et al., 1967): approximately one third of essential hypertensives responded to head-up tilting with a reduced rise in total peripheral vascular resistance and postural hypotension. Whether reduced reflex sympathetic activity in hypertensives with such an "orthostatic hypotensive" response is related to the phenomenon of low-renin hypertension has not been investigated.

This possibility has been tested in the present study, in which urinary catecholamine excretion and plasma renin activity have been measured concurrently, at rest and with head-up tilting, insulin hypoglycaemia, and mental stress, in patients with essential hypertension and subjects with normal BP.

**METHODS**

Forty-one untreated hypertensive patients (31 sustained essential hypertension, 10 borderline hypertension) and
20 normotensive subjects were studied. The sympathetic nervous system responsiveness to tilting in 33 of the hypertensives and 9 of the subjects with normal BP has been described previously in Chapter 3. Of the hypertensives, 34 had received no previous treatment for the hypertension, while 7 had received treatment in the past, though not in the preceding 12 months. The blood pressure elevation was designated sustained hypertension or borderline hypertension on the basis of average casual or "usual" BP (Chapter 3). Secondary hypertension was reasonably excluded by routine screening procedures including urine microscopy and culture, serum and 24-hour urinary sodium and potassium levels, endogenous creatinine clearance, urinary catecholamine excretion, and in most cases intravenous pyelography (no intravenous pyelogram in 5 patients with borderline hypertension). None of the female hypertensives was taking oral contraceptive drugs. The 20 normotensive subjects comprised 9 student volunteers and 11 ambulant general medical patients. None had cardiovascular or renal disease, or a family history of hypertension.

The investigations were performed on the hypertensives as outpatients (25 subjects), or during the first three days of hospital admission (16 subjects) to minimize any effects of confinement and prolonged recumbency (Dietrick et al., 1948). Subjects were maintained on an unrestricted diet, and fasted overnight before each procedure.

**EXPERIMENTAL PROCEDURES**

*Head-up tilting.* The changes in blood pressure, urinary catecholamine excretion, creatinine clearance, plasma
renin activity, and urinary sodium excretion with 25° head-up tilting were measured in the 41 patients with hypertension and 12 subjects with normal BP. The experimental procedure was as outlined in Chapter 3. In addition, peripheral venous blood was drawn at the end of the period of supine rest and after 90 minutes of tilt, for assay of plasma renin activity. Urine was also collected at both these times, and stored prior to the estimation of sodium concentration.

**Insulin Hypoglycaemia.** The change in blood pressure, urinary catecholamine excretion, plasma renin activity, plasma volume, and creatinine clearance with insulin-induced hypoglycaemia was studied in 6 hypertensive patients, and 6 subjects with normal BP. The experimental procedure was as follows: A 21 G scalp-vein needle was inserted in an arm vein 60 minutes prior to commencing the study, and the catheter kept open with a slow infusion of 0.9% saline. Subjects were then rested flat for one hour, at the end of which they emptied their bladder. The experiment comprised 2 test periods; 90 minutes of supine rest, and then following the injection of soluble insulin, 0.03 u/Kg, a further 120 minutes. Urine was collected at the end of both these periods, acidified, and frozen for storage prior to the estimation of urinary free catecholamines and creatinine. Blood pressure was measured with a sphygmomanometer at 10-minute intervals during the pre-insulin period, and at 5-minute intervals thereafter. Venous blood was withdrawn via the catheter, for estimation of blood glucose, immediately prior to the administration of insulin, and at 15, 30, 45, 60, and 120 minutes
post-insulin. Blood sampling for the estimation of serum creatinine and PRA was performed immediately before the administration of insulin, and again 45 minutes post-insulin. Plasma volume was measured twice, with Evans Blue, during the pre-insulin period, and at 60 minutes post-insulin.

**Mental Stress.** The effect of an anxiety-provoking situation on blood pressure, urinary catecholamine excretion, and PRA was studied in 10 hypertensive patients and 6 subjects with normal BP. The procedure used was that of Nestel (1969), in which solving visual puzzles against the clock constitutes the stimulus. The experiment comprised 2 test periods; 90 minutes of supine rest, followed by a 2-hour period which commenced with 45 minutes of "mental stress". Urine was collected for assay of catecholamines and creatinine at the end of both periods. Blood pressure was measured with a sphygmomanometer during the pre-stress period, and throughout the 45 minutes of mental stress, and the mean BP response calculated. Venous blood was withdrawn twice for the estimation of plasma renin activity and serum creatinine, at the end of the pre-stress period, and after 45 minutes of problem-solving.

Urinary free noradrenaline and adrenaline were assayed in duplicate by a modification of the trihydroxyindole method (Crout, 1961) with differential fluorimetry using 2 sets of filters (von Euler and Lishajko, 1959). Urinary creatinine was measured by a modification of the alkaline picrate method (Edwards and Whyte, 1958), serum creatinine was measured by autoanalyzer. From the serum creatinine concentration and urinary creatinine excretion, endogenous
creatinine clearance was calculated. Urinary noradrenaline and adrenaline excretion was adjusted for within-group differences in GFR, and for incomplete emptying of the bladder, as follows:

Adjusted catecholamine excretion (µg catecholamine/litre of plasma cleared of creatinine) = catecholamine excretion (µg/min)/GFR (litre/min). The validity of this adjustment is discussed in Chapter 2 and 7.

Plasma renin activity was measured using the bioassay method of Skinner (1967). Urinary sodium concentration was estimated by flame photometry. Blood glucose concentration was estimated using the glucose oxidase method (Huggett and Nixon, 1957).

RESULTS

Resting Values of Noradrenaline, Adrenaline, PRA.

Plasma renin activity at rest was similar in the 41 hypertensive patients and the 20 subjects with normal BP, 1.23 ± 0.76 ng/ml/hr (mean ± standard deviation) in the hypertensives compared with 1.18 ± 0.34 ng/ml/hr in the normotensives. Urinary adrenaline excretion was also similar in the hypertensives (0.08 ± 0.06 µg/1) and the subjects with normal BP (0.07 ± 0.05 µg/1). Mean urinary noradrenaline level was significantly higher in the hypertensives; 0.25 ± 0.12 µg/1 compared with 0.18 ± 0.07 µg/1 (p < 0.05). Plasma renin activity was not related to either urinary adrenaline or urinary noradrenaline excretion in either group.

Response to Head-up Tilting. The mean changes in diastolic blood pressure, urinary noradrenaline, PRA, and GFR on tilting were similar in hypertensive and normotensive
subjects. There was a rise in diastolic BP of 4.9 ± 6.8 mmHg in hypertensives (p < 0.01, paired t-test) and 5.1 ± 3.4 mmHg in normotensive subjects (p < 0.05) on tilting. Change in noradrenaline level in hypertensives was + 0.08 ± 0.11 µg/l (p < 0.01), and in normotensives + 0.05 ± 0.05 µg/l (p < 0.05). The PRA response was + 0.27 ± 0.31 ng/ml/hr in patients with hypertension (p < 0.01), and + 0.34 ± 0.24 ng/ml/hr in subjects with normal BP (p < 0.01). Glomerular filtration rate fell with tilting in both groups, by 10.0 ± 17.4% in hypertensives (p < 0.01) and by 7.5 ± 13.8% in the normotensive subjects (p < 0.05). The mean responses in the 2 groups were not significantly different.

The noradrenaline and renin response in the hypertensive subjects was positively correlated; r = + 0.69, p < 0.01, Fig. 4-1. Among the 12 subjects with normal BP there was also a trend for change in PRA and noradrenaline to correlate directly, but the correlation was of low order and not significant (r = + 0.34, Fig. 4-1). The change in PRA was not related to changes in GFR or urinary sodium excretion in either group.

Twelve of 41 patients with essential hypertension who showed a rise in diastolic BP of 11 mmHg or more, or an increase in urinary noradrenaline greater than 0.15 µg/l in response to tilting, were categorized as "sympathetic hyperresponders" on the basis of rises in blood pressure or noradrenaline above the range of responses observed in the normal subjects (Chapter 3). In 7 of these 12, both blood pressure and noradrenaline response were above the normal range. Plasma renin activity at rest was higher
in this group than in the normotensive subjects; 1.80 ± 0.90 ng/ml/hr compared with 1.14 ± 0.38 ng/ml/hr (p < 0.05, Fig. 4-2). The increase in PRA with tilting was also greater, 0.56 ± 0.21 ng/ml/hr compared with 0.34 ± 0.24 (p < 0.05).

PRA with tilting was 1.48 ± 0.41 ng/ml/hr in the subjects with normal BP. Six of the essential hypertensives, with a PRA of less than 0.66 ng/ml/hr after 90 minutes of head-up tilt, had a renin level more than 2 standard deviations below the mean PRA during tilting in the normotensive subjects, and were categorized as "low-renin essential hypertensives". This group tended to have diminished sympathetic responsiveness to tilting, with smaller rises in noradrenaline level and blood pressure, and a smaller fall in GFR than occurred in the subjects with normal BP, or the hypertensive group as a whole (Fig. 4-2).

It was anticipated that the "sympathetic hyperresponders", with larger rises in PRA and greater falls in GFR, might display a greater degree of sodium retention with tilting than the other hypertensives, but this was not confirmed (Fig. 4-3).

Response to Hypoglycaemia. Although the fasting blood glucose level prior to insulin was higher in the hypertensive subjects (p < 0.05, Fig. 4-4), the mean maximal falls with insulin, 49 ± 8 mg% in hypertensives and 36 ± 13 mg% in normotensive subjects, and the minimum blood glucose levels, 37 mg% in patients with hypertension and 35 mg% in subjects with normal BP, were not significantly different (Fig. 4-4). The hypoglycaemia was associated with an increase in pulse rate and a fall in diastolic BP in
both groups, and in the subjects with normal BP, a rise in systolic blood pressure (Fig. 4-4). The rise in adrenaline level in the hypertensive subjects was similar to that in normotensive subjects, 0.25 ± 0.13 μg/l compared with 0.22 ± 0.15 μg/l. Noradrenaline level did not change significantly (Fig. 4-5). There were small rises in PRA in both groups, + 0.22 ± 0.11 ng/ml/hr in the hypertensives and + 0.13 ± 0.30 ng/ml/hr in the subjects with normal BP. The rise in PRA was statistically significant in hypertensives only (p < 0.05, paired t-test). Plasma volume increased with hypoglycaemia in both groups, from 16.4 ± 1.5 cc/cm to 18.6 ± 1.7 cc/cm in normotensive subjects (p < 0.05, paired t-test), but only marginally in hypertensives, from 17.2 ± 2.1 cc/cm to 18.2 ± 1.8 cc/cm (difference not significant).

Response to Mental Stress. There were significant rises in systolic and diastolic BP during mental stress in both hypertensive and normotensive subjects (p < 0.01, Fig. 4-6). The rises were of similar magnitude in both groups. The urinary adrenaline level rose significantly, from 0.06 ± 0.06 μg/l to 0.12 ± 0.06 μg/l in both hypertensive and normotensive subjects (p < 0.05). There were no significant changes in noradrenaline level or PRA (Fig. 4-6).

Comparison of the Adrenergic Responsiveness of Hypertensives to the Different Stimuli. Among the hypertensive subjects, there was no tendency for the sympathetic hyperresponders to tilt, who had an enhanced noradrenaline response to this stimulus, to display larger
than normal adrenaline responses to the other stimuli of hypoglycaemia and mental stress (Fig. 4-7).

DISCUSSION

In this study, a relationship was noted between reflex sympathetic nervous system responsiveness to tilting, and both the resting level of plasma renin activity and the renin response to tilting. Essential hypertensives exhibit a broad range of sympathetic nervous responsiveness when tilted, extending from the enhanced blood pressure and noradrenaline response of sympathetic hyperresponders, through to sympathetic underresponsiveness characterized by postural hypotension and negligible noradrenaline response (Fröhlich et al., 1967; Chapter 3). The determinants of reflex sympathetic responsiveness to change in posture are incompletely understood, but response appears to be inversely related to the severity of the hypertensive disease (Chapter 3). Sympathetic hyperresponders to tilt were found to have elevated resting PRA levels and the largest rises in PRA with tilting, while patients with low-renin essential hypertension, characterized by a suppressed PRA level at rest and with stimulation, showed sympathetic underresponsiveness to tilting. Overall, there was therefore a close correlation between the renin and noradrenaline response to tilting.

There is strong evidence that the renin response to the upright posture is mediated through the sympathetic nervous system (Oparil et al., 1970; Winer et al., 1969; Michelakis and McAllister, 1972). It is likely that differences in levels of PRA at rest, and renin
responsiveness to tilting observed here were a consequence of differences in reflex sympathetic nervous activity in the hypertensive population studied. But another possible interpretation is that the relationship may be working in the reverse direction, through renin-angiotensin status influencing sympathetic nervous system activity. There is a considerable body of evidence supporting such a possibility, recently reviewed by Ferrario et al. (1972). Peripheral and central effects of angiotensin in enhancing sympathetic nervous function have been well documented in animals, and increased sympathetic responsiveness has been described in renovascular hypertension in man (Frohlich et al., 1967(a)).

The reduced sympathetic responsiveness noted in low-renin essential hypertensives could possibly be the basis of the suppression of renin release which characterizes this disorder, but a more likely interpretation is that the reduced sympathetic and renin responsiveness both reflect retention of sodium, with the sympathetic nervous system having no primary role in determining renin status. Sympathetic nervous activity is influenced by the level of dietary sodium in normal subjects, being greatest with sodium deprivation (Gordon et al., 1967). Reduced sympathetic responsiveness has been described in primary aldosteronism (Biglieri et al., 1962). Total body exchangeable sodium is increased in low-renin essential hypertension (Woods et al., 1969), and there is much indirect evidence implicating mineralocorticoid excess in the pathogenesis of this disorder (Crane et al., 1972).

Both insulin-induced hypoglycaemia and mental stress were found to be poor stimuli for renin release. Although hypoglycaemia produced a large adrenaline response, of
similar magnitude in hypertensive and normotensive subjects, the rise in plasma renin activity was small, and statistically significant only in the hypertensives. Insulin hypoglycaemia has been shown to considerably elevate PRA in the dog (Otsuka et al., 1970). The increase in plasma volume with hypoglycaemia may perhaps have been responsible for the smaller response observed in this study. With mental stress, blood pressure and urinary adrenaline excretion increased to a similar degree in hypertensive and normotensive subjects. These results are at variance with those of Nestel (1969), who described an exaggerated blood pressure and catecholamine response to mental stress in borderline hypertension. In the present investigation, 8 of 10 subjects studied had sustained hypertension; the discrepancy in the findings may have resulted from the different composition of the groups studied. In both hypertensive and normotensive subjects, the stressful problem-solving procedure was without effect on PRA. The relative ineffectiveness of hypoglycaemia and mental stress as renin-releasing stimuli may be related to the fact that with both, unlike head-up tilting, the predominant catecholamine response involves adrenaline. From studies in the dog (Johnson et al., 1971), it would appear that adrenaline has no direct effect on renin release, the renin response with adrenaline resulting from a diminution in renal blood flow. In contrast, noradrenaline and renal sympathetic nerves have direct effects, independent of altered renal haemodynamics.

A subgroup of essential hypertensives has been described who display enhanced sympathetic nervous system and renin
responsiveness to head-up tilting. Whether the larger posture-related rises in PRA and falls in GFR in these sympathetic hyperresponders are of pathogenic significance is not known. It was thought that with repeated stimulation by the upright posture, the larger changes in PRA and GFR might provide a potential mechanism for sodium retention and elevation of blood pressure. However, the acute reduction in urinary sodium excretion on tilting was no greater in this group than in other essential hypertensives. These tilt hyperresponders do not have a generalized sympatho-adrenomedullary overresponsiveness to adrenergic stimulation. Their responses to hypoglycaemia and mental stress were within normal limits.
Figure 4-1. The relationship between changes in urinary noradrenaline excretion and plasma renin activity with 25° head-up tilt. For the hypertensive subjects, $r = +0.69$, $p < 0.01$. 
Figure 4-2. The sympathetic nervous system and renin responses to 25° head-up tilting in essential hypertensives and subjects with normal BP.
Figure 4-3. The effect of 25° head-up tilting on urinary sodium excretion in patients with essential hypertension.
Figure 4-4. Changes in blood pressure, pulse rate, and blood glucose level in hypertensive and normotensive subjects during the course of insulin-induced hypoglycaemia.
Figure 4-5. The effect of insulin-induced hypoglycaemia on urinary catecholamine excretion, plasma renin activity, creatinine clearance, and plasma volume in hypertensive and normotensive subjects.
Figure 4-6. The changes in blood pressure, urinary catecholamine excretion, and plasma renin activity with "mental stress" in hypertensive and normotensive subjects.
The catecholamine response to head-up tilt, hypoglycaemia, and mental stress in essential hypertensive patients categorized on the basis of sympathetic responsiveness to tilting.
CHAPTER 5
EVALUATION OF PRACTOLOL IN HYPERTENSION: EFFECTS ON SYMPATHETIC NERVOUS SYSTEM AND RENIN RESPONSIVENESS

SUMMARY

The β-adrenergic blocker, practolol, proved to be an effective antihypertensive agent in a single-blind crossover trial, involving 17 patients with essential hypertension of mild to moderate severity. After a 2-month placebo period, dosage was commenced at 100 mg bd, and titrated against blood pressure response up to a maximum dose of 400 mg bd, leading to an average reduction in BP of 20/18 mmHg, and satisfactory control in 14 of 16 patients (one defaulter). The clinical and physiological data were analyzed for prediction of response to practolol. The urinary noradrenaline response to head-up tilt, an index of the responsiveness of the sympathetic nervous system, correlated significantly with subsequent BP reduction with practolol 100 mg bd (r = 0.62, p < 0.01). In 8 patients, responsiveness to tilt was retested after control of the BP; changes in diastolic BP and pulse rate while on practolol were both significantly less than pre-treatment responses. The urinary noradrenaline response was also reduced (+0.50 μg/hr vs. pre-treatment mean of +1.64 μg/hr; p < 0.01), a finding not explicable in terms of known receptor-blocking properties of the drug. It is suggested that the antihypertensive action of β-adrenergic blockers may be related to a reduction in the reflex activity of the sympathetic nervous system.
Plasma renin activity, which was normal in the recumbent state, rose with tilting. The response with tilt was significantly reduced with practolol, although PRA during recumbency was only marginally lowered by the drug.
INTRODUCTION

Although β-adrenergic blocking drugs are finding increasing application in the treatment of hypertension, the mechanism by which they lower blood pressure remains uncertain. The antihypertensive effect has been attributed to a reduction in cardiac output (Frohlích et al., 1968), but a satisfactory reduction in blood pressure with oral medication has been stated to occur after a latent period of several weeks (Prichard and Gillam, 1969), whereas the effect on cardiac output is rapid. An unexplained phenomenon is the extreme range of sensitivity to the BP-lowering effects of β-blockers shown by essential hypertensives, dose requirements of propranolol varying between perhaps 0.1 and 3 g daily (Zacharias, 1971; Prichard, 1970).

Essential hypertensives exhibit a broad range of sympathetic nervous system responsiveness when subjected to postural stresses, extending from underactivity in patients responding to tilting with postural hypotension, through to increased activity in so-called "orthostatic hypertensives" who display greater than normal rises in blood pressure (Frohlích et al., 1967) and noradrenaline (Chapter 3). The relationship between sympathetic responsiveness to change in posture and subsequent sensitivity to the BP-lowering effect of a β-adrenergic blocker has been investigated.

Oral administration of propranolol produces a fall in blood pressure which is associated with a reduction in cardiac output, but total peripheral vascular resistance is increased (Frohlích et al., 1968).
contribution of reflex vasoconstriction and blockade of $\beta$-adrenergic vasodilator receptors in skeletal muscle to this rise in vascular resistance is not clear. The "cardioselective" $\beta$-adrenergic blocker, practolol, has a lesser effect on vessels in skeletal muscle than propranolol (Barrett, 1971). This might be advantageous in the treatment of hypertension, and the efficacy of practolol as an antihypertensive agent has been assessed in the present study.

**PATIENTS AND METHODS**

**Patients**

The study was performed on 17 patients (8 male, 9 female), average age 38 years (range 21-56), with essential hypertension. All had sustained hypertension of mild to moderate severity. Average pre-treatment blood pressure was 164/107 mmHg (range 150/95 - 180/118), and severity index (Corcoran et al., 1954) 2.5 (range 0 - 4.0). The diagnosis of essential hypertension was reasonably established by routine screening tests including urine microscopy and culture, serum and 24 hour urinary sodium and potassium, endogenous creatinine clearance, urinary catecholamines, and intravenous pyelography. None of the female patients was taking oral contraceptive drugs. The majority of the patients had received no previous treatment for hypertension; 4 had been treated in the past, but not in the preceding 12 months. No patient with a history of bronchospasm, Raynaud's phenomenon, or cardiac failure was included in the study.
Laboratory Investigations

Changes with tilting in blood pressure, urinary noradrenaline (corrected for changes in GFR) and plasma renin activity were measured. The experimental procedure was as follows: after an overnight fast, subjects were rested supine in a single-bed ward for 90 minutes prior to the commencement of the study, at the end of which they emptied their bladder. Smoking was forbidden, and drinking water was given throughout to ensure an adequate urine flow. Then, after 90 minutes of recumbent rest, a timed urine sample was collected for assay of catecholamines and creatinine. Blood was drawn at this stage, after 3 hours of recumbency, for assay of serum creatinine and plasma renin activity. When blood pressure had stabilized after the venepuncture, the patients were tilted head-up at 25° on a tilt-table for a further 90 minutes. Blood pressure was measured at frequent intervals with a sphygmomanometer with the cuff at heart level. At the end of this period of tilt, further samples of blood and urine were collected for assay of catecholamines, creatinine, and plasma renin activity.

Urinary free noradrenaline and adrenaline were determined in duplicate using the method of Crout (1961) by differential fluorimetry using 2 sets of filters (von Euler and Lishajko, 1959).

Urinary creatinine was measured by a modification of the alkaline picrate method (Edwards and Whyte, 1958), serum creatinine by autoanalyzer.

Plasma renin activity was determined by the bioassay method of Skinner (1967) using the anaesthetized
The difference between 24 duplicate measurements of PRA was 6 ± 9% (mean ± standard deviation). The assay was performed in duplicate on 2 different rats, and was repeated if duplicates differed by more than 24% (mean difference + 2 S.D.).

Drug Trial Design

The antihypertensive effect of practolol was evaluated in a single-blind crossover trial in which a placebo was given for 2 months, followed by a fixed dose of practolol, 100 mg bd, for 6 months. The dose was then titrated against blood pressure response up to a maximum dose of 400 mg bd. The pre-treatment BP value was the mean of 4 readings obtained from second-weekly outpatient attendances over the 2 months on placebo. There was no fall in BP during this time. The treatment BP on the 100 mg bd dose schedule was the mean of all outpatient readings taken at intervals of 2 to 3 weeks over the last 4 months of the 6 month period on practolol. If the recumbent BP exceeded 150/90 mmHg after 6 months, the dose was increased until the BP was reduced to this level, or until an arbitrary maximum dose of 400 mg bd was being given. Lying blood pressures were measured, by a single observer with a sphygmomanometer bag dimensions 30 x 12.5 cm, after 3-5 minutes of recumbent rest. Standing blood pressures were measured after the patient had been standing for 1-2 minutes.

RESULTS

The effect of practolol 100 mg bd on pulse rate and supine and standing blood pressures is shown in Table 5-1. Significant reductions in systolic and diastolic BP and
pulse rate occurred on the drug. The falls in supine and standing pressures were of similar magnitude.

Practolol proved to be clinically effective as the sole antihypertensive agent in these patients with mild to moderately severe sustained hypertension. Using a recumbent BP of 150/90 mmHg as a therapeutic endpoint, in 7 of 17 patients control was achieved with a dose of 100 mg bd, a further 5 required 200 mg bd, and another 2 patients 400 mg bd. Since there was one defaulter, a dose of up to 400 mg bd resulted in satisfactory control in 14 of 16 patients. At the upper dose level the mean reduction in recumbent BP was 20/18 mmHg.

The drug was well tolerated and in particular there were no recorded instances of postural or exercise-induced hypotension. A maculopapular rash, constipation, lethargy, and vivid dreams was each observed once, but did not require treatment to be stopped.

The rate of fall of BP on a constant dose of 100 mg practolol twice daily is shown in Fig. 5-1. In the 7 patients who were controlled on this dose, the maximum fall in BP had virtually been attained by the time of the first outpatient attendance after 2 weeks of treatment (Fig. 5-1). There were no delayed falls in these patients, or in the others with smaller initial responses to this dose. On recommencing the placebo, the return of the BP to pre-treatment levels was slow, taking of the order of 4 to 6 weeks (Fig. 5-1; BP 147/95 mmHg after 2 weeks off practolol vs. 162/102 mmHg after 6 weeks off practolol; p < 0.01 for paired t-test).
Some essential hypertensives are very sensitive to the BP-lowering effects of β-adrenergic blockers. We tried to categorize these retrospectively on clinical and physiological grounds. Some indices did not predict sensitivity to practolol. BP reduction on the low dose was unrelated to the initial level of the blood pressure (within the narrow range encompassed in this study), severity index, resting pulse rate, plasma renin activity, or the supplemental blood pressure (Smirk, 1954), (casual BP minus basal BP, a measure of the lability of the hypertension). The sympathetic responsiveness to head-up tilt did, however, correlate with subsequent BP reduction with practolol. When subjected to head-up tilt, essential hypertensives exhibit a broad range of sympathetic responsiveness, ranging from greater noradrenaline and BP responses than occurring in normotensive subjects through to normal or diminished responsiveness (Frohlich et al., 1967; Chapter 3). The hyperresponders to tilt, with greater than normal noradrenaline and BP responses, proved to be most sensitive to the BP-lowering effects of practolol at the lowest dosage. Overall there was a significant correlation between the urinary noradrenaline response to tilt and subsequent BP reduction (r = 0.62, p < 0.01; Fig. 5-2). The correlation between diastolic BP response to tilt and subsequent BP reduction on practolol was of a lower order (r = 0.42, 0.1 > p > 0.05), but "orthostatic hypertensives", with a diastolic BP rise of > 10 mmHg (Chapter 3), as a group had a larger fall in mean BP than the hypertensives with normal or reduced BP responses to tilt (fall in mean BP 23.1 ± 11.7 mmHg vs. .
In 8 patients, in whom the BP had been satisfactorily controlled with either 200 mg (7) or 400 mg (1) daily, the responses to tilting were retested after an interval of 9-24 months. The BP, pulse rate, and urinary noradrenaline responses were all significantly diminished (Fig. 5-3). Five of these patients were recommenced on placebo, and after an interval of 2-3 months during which BP's rose to near pretreatment levels, responses were measured a third time. Tilt responses on placebo, including the noradrenaline response, were greater than on practolol, and had returned towards pretreatment figures (Fig. 5-3).

In 8 patients the effect of practolol on plasma renin activity was measured. PRA was measured after 3-4 hours of recumbent rest, and after 90 minutes of 25° head-up tilt, once before treatment, and again on practolol. There was no restriction of dietary sodium intake in these patients. Although big falls in unstimulated PRA occurred with practolol in the 3 patients in whom it was initially high, the difference overall was not significant at the 5% level; 1.91 ± 0.46 ng/ml/hr (mean ± standard deviation) vs. 1.25 ± 0.34 on practolol; 0.05 < p < 0.1 paired t-test. The PRA response to tilt was significantly diminished on practolol (Fig. 5-4; p < 0.01).

DISCUSSION

The antihypertensive effect of oral propranolol therapy is associated with a fall in cardiac output, but total peripheral vascular resistance is elevated (Frohlich et al., 1968). Because practolol has much less activity
on β-adrenergic peripheral vasodilator receptors in skeletal muscle than propranolol (Barrett, 1971), and chronic oral administration of practolol is not associated with increase in total vascular resistance (Bodem et al., 1971), it was anticipated that practolol too would lower blood pressure in essential hypertension, and perhaps be more potent in this regard than propranolol. In this trial, practolol proved to be an effective antihypertensive agent in patients with moderate sustained essential hypertension. A similar finding has been reported by 2 other groups of workers (Prichard et al., 1971; Waal-Manning, 1970). The antihypertensive activity relative to that of propranolol remains uncertain. In the only comparative trial (Waal-Manning, 1970), propranolol and practolol were found to be of similar potency, but since a 2-week crossover design had been used, a residual effect on blood pressure from the previous β-adrenergic blocker may still have been present when the second drug was being evaluated.

As has been found previously with propranolol (Zacharias, 1971; Prichard, 1970), the essential hypertensive patients exhibited a broad range of sensitivities and hence dose requirements, although pre-treatment blood pressures were similar. Sensitivity to the blood pressure lowering effect of practolol was unrelated to such variables as the resting pulse rate, and the supplemental BP, a measure of the lability of the hypertension. Only the sympathetic responsiveness to head-up tilt correlated with subsequent sensitivity to practolol. The haemodynamic and noradrenaline response to change in posture was used as an index of "sympathetic
nervous activity". The urinary noradrenaline response is probably a qualitatively valid if quantitatively inexact index of change in sympathetic activity, and might reflect baroreceptor sensitivity, and the activity of central noradrenergic neurones and peripheral sympathetic nerves. When responsiveness to tilt was reassessed in 8 patients on practolol (7 of whom had previously reacted as tilt hyperresponders), response in all was reduced to within the normal range. The fall in the noradrenaline response is not readily explicable in terms of known receptor-blocking properties of the drug.

The mechanism by which practolol produced this reduction in reflex sympathetic activity is unknown. An increase in blood volume can reduce orthostatic responsiveness (Jeffrey et al., 1970). Blood volume was not altered by practolol in 3 patients in whom it was measured, and in fact, reduction in plasma volume with propranolol has recently been reported (Tarazi et al., 1971). Although there is some indirect evidence of a reduction in baroreceptor sensitivity by propranolol in dogs (Booker et al., 1969), observations in man do not support this finding (Sleight et al., 1971). An effect on central noradrenergic neurones is a possible explanation since the occasional side-effect of troublesome dreams (Wiseman, 1971) suggests that practolol enters the central nervous system. What relation, if any, this reduction in reflex sympathetic nervous system activity has to the antihypertensive action of the drug is uncertain, but it has often been suggested that repeated, greater than normal, reflex responses to
pressor stimuli occurring in borderline hypertension may contribute to the genesis of sustained hypertension.

The search for the best existing drug for a particular patient with essential hypertension is largely a matter of trial and error. With β-blockers, the main therapeutic guideline relates to the exclusion of certain patients, such as those with uncontrolled heart failure or a history of bronchospasm, there being no clear-cut grounds for preferring this class of drugs to another. Subgroups of patients with essential hypertension may exist who would be expected to be highly sensitive to β-adrenergic blockers, such as those with "hyperdynamic β-adrenergic disease" (Frohlich et al., 1969), in whom a raised blood pressure is associated with cardiac symptoms, such as palpitations, and excessive sensitivity to infused β-agonist can be demonstrated. The orthostatic hyperresponders described in this study may prove to be another group in whom a β-blocker might be a logical first line drug, although it is clear that with adequate dosage, satisfactory control can be achieved in the majority of hypertensive patients (Zacharias, 1971; Prichard, 1970).

It has been suggested that other physiological variables, such as plasma renin activity and cardiac output, may be relevant to the different sensitivity shown by individual hypertensive patients to β-adrenergic blockers. While cardiac output was not measured, evidence exists that orthostatic hypertensives have a higher than average cardiac output (Frohlich et al., 1967). In the present study, recumbent PRA before treatment did not correlate with subsequent BP reduction on the low dose of practolol.
The effect of practolol on plasma renin activity is of interest. Unlike propranolol, which has been demonstrated to lower PRA (Stokes et al., 1970), practolol did not significantly reduce recumbent PRA. However, the renin response to tilt was diminished by practolol. The sympathetic nervous system may be involved in the release of renin (Vander, 1967), including the renin release with upright posture (Winer et al., 1969). The work in Chapter 4 suggests that renin responsiveness to head-up tilting is related to sympathetic nervous system responsiveness. The diminished renin response to tilt during practolol therapy may reflect only the diminished reflex sympathetic responsiveness.
### TABLE 5-1
Mean Response to Practolol 100 mg b.d.

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Practolol</th>
<th>Significance Level*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>100 mg bd</td>
<td>Reduction</td>
<td></td>
</tr>
<tr>
<td><strong>Supine</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>164</td>
<td>148</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>107</td>
<td>94</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P &lt; 0.01</td>
</tr>
<tr>
<td>Pulse Rate/min</td>
<td>80</td>
<td>70</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td><strong>Standing</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP</td>
<td>160</td>
<td>146</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P &lt; 0.01</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>111</td>
<td>98</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P &lt; 0.001</td>
</tr>
</tbody>
</table>

* paired t-test.
Figure 5-1. Average outpatient blood pressure, in 7 patients whose elevation of BP was controlled by a practolol dose of 100 mg twice daily, during intervals on (i) Placebo (ii) Constant dose of practolol (iii) Placebo. Means and standard errors are shown.
Figure 5-2. Relationship of pre-treatment urinary noradrenaline response to 25° head-up tilt in 17 patients with essential hypertension, to subsequent fall in Mean BP* produced by a practolol dose of 100 mg twice daily; 

\[ r = +0.62, \ p < 0.01. \]

(* Mean BP = 1/3 systolic BP + 2/3 diastolic BP).
Figure 5-3. Average outpatient diastolic BP and responses in pulse rate, diastolic BP, and urinary noradrenaline to 25° head-up tilt, in essential hypertensive patients before treatment, after control of the BP by practolol, and on return to a placebo. Mean values and significance levels (paired t-test) are shown.
Figure 5-4. The effect of oral practolol on the increase in plasma renin activity with tilting. The PRA response was significantly reduced on practolol (p < 0.01).
CHAPTER 6

THE EFFECT OF PRACTOLOL ON THE RELEASE

OF RENIN BY ISOPRENALINE

SUMMARY

The effect of the β-adrenergic blocking drug, practolol, on the heart rate and plasma renin responses to a graded isoprenaline infusion has been studied in normal subjects. A dose of practolol which produced a 50-60% reduction in the heart rate response to isoprenaline was without effect on the renin response.
Reduced renin responsiveness to tilting was noted in essential hypertensive patients treated with the \( \beta \)-adrenergic blocking drug, practolol (Chapter 5). Plasma renin activity (PRA) at rest was not significantly altered by long-term oral dosage of the drug. The responsiveness of the sympathetic nervous system to tilting was also reduced in these patients, providing a possible basis for the reduced renin responsiveness. An alternative explanation is that the reduced renin release may have been related to direct receptor-blocking properties of the drug. The acute effects of practolol on the release of renin by isoprenaline has been studied to investigate this second possibility.

The infusion of isoprenaline into normal dogs (Winer et al., 1971), and dogs with experimental renovascular stenosis (Ayers et al., 1969), causes an increase in renin secretion. The renin response presumably results from direct effects of isoprenaline on juxtaglomerular cells, such as has been demonstrated with adrenaline and noradrenaline \textit{in vitro} (Michelakis et al., 1969), and is unrelated to changes in arterial pressure and renal blood flow (Winer et al., 1971; Ayers et al., 1969). The renin response to isoprenaline is abolished by prior injection of propranolol (Winer et al., 1971; Ayers et al., 1969).

Practolol differs from propranolol in its range of action. Its receptor-blocking activity is mainly confined to \( \beta_1 \)-adrenoceptors of the heart (Barrett, 1971).
direct effect of "relatively cardioselective" practolol on renin release has not been studied previously.

**METHODS**

The renin response to a graded infusion of isoprenaline, and the effect of a prior injection of 20 mg of practolol on this response, was studied in 5 normal subjects. The subjects were healthy student volunteers, on an unrestricted diet. After an overnight fast, subjects were rested flat for 3 hours prior to commencing the test. A 21 G scalp vein needle was inserted in an arm vein one hour before the first sample of venous blood was to be drawn, and the catheter kept open with a slow infusion of 0.9% saline. Isoprenaline was infused twice in each subject, the infusions being 2 days apart. One hour prior to commencing the infusion, either practolol 20 mg, or 10 cc of 0.9% saline was slowly injected intravenously, the order being randomized. Isoprenaline HCl (Winthrop) dissolved in saline, was infused with a Braun infusion pump at rates of 10, 20, and 30 ng isoprenaline base/Kg/min, each for 30 minutes (Fig. 6-1). 15 cc of venous blood, for assay of PRA, was withdrawn via the catheter immediately before the injection of practolol or placebo, prior to commencing the infusion, and every 30 minutes during the infusion. The blood was chilled then centrifuged, and the plasma frozen and stored at -20°C prior to estimation of PRA. Heart rate was measured at 5-minute intervals during the period of infusion. The mean figure at which heart rate stabilized at each dose level was calculated. Blood loss from venous sampling throughout the
study was 75 cc. This was replaced by approximately the same volume of 0.9% saline, amounting to 10 meq. of sodium, given over the total 3\text{\frac{1}{2}} hours of the experiment.

Plasma renin activity was estimated by the bioassay method of Skinner (1967), using the anaesthetized ganglion-blocked rat.

**RESULTS**

The effect of practolol, 20 mg intravenously, on blood pressure, pulse rate, and PRA at rest is shown in Table 6-1. No changes were produced by the drug, including in PRA, which was $0.67 \pm 0.26$ ng/ml/hr (mean ± standard deviation) before practolol and $0.62 \pm 0.21$ 60 minutes after practolol.

The changes in heart rate and PRA with isoprenaline, and the effect of practolol on these changes, are shown in Table 6-2 and Fig. 6-1. Isoprenaline produced increases in heart rate of $23 \pm 4$, $43 \pm 8$, and $61 \pm 10$ per minute at rates of 10, 20, and 30 ng/Kg/min respectively. After practolol, the corresponding increases in heart rate were $11 \pm 3$, $18 \pm 5$, and $30 \pm 3$ per minute, equivalent to reductions of 52%, 58%, and 51% in the heart rate response to isoprenaline.

There were dose-related rises in PRA during the infusion of isoprenaline. Rises of $0.41 \pm 0.23$ ng/ml/hr ($p < 0.05$; paired t-test), $0.67 \pm 0.35$ ($p < 0.01$) and $0.76 \pm 0.31$ ($p < 0.01$) occurred at infusion rates of 10, 20, and 30 ng/Kg/min respectively. After practolol, the corresponding rises in PRA were $0.28 \pm 0.17$ ($p < 0.05$), $0.51 \pm 0.18$ ($p < 0.01$), and $0.74 \pm 0.17$ ($p < 0.01$). The increase in PRA produced by isoprenaline was not
significantly different, with and without practolol, at any of the 3 rates of administration of isoprenaline.

**DISCUSSION**

In this study, isoprenaline was noted to increase peripheral venous PRA in man. There have been previous reports that isoprenaline increases the secretion of renin in dogs (Winer *et al.*, 1971; Ayers *et al.*, 1969). Infused adrenaline and noradrenaline (Michelakis and Horton, 1970) and catecholamines endogenously released during hypoglycaemia (Otsuka *et al.*, 1970), have been shown to increase PRA in man.

The mechanism by which sympathomimetic amines cause secretion of renin is not entirely clear. The relative importance of changes in arterial pressure, renal blood flow, and distal renal tubular sodium concentration, and direct stimulation of the juxtaglomerular cells, probably differs in relation to the particular agonist properties of the agent under consideration (Johnson *et al.*, 1971). From studies in the dog it would appear that the main effect of isoprenaline is a direct one on juxtaglomerular cells. The renin response to isoprenaline is unrelated to changes in arterial pressure and renal blood flow (Winer *et al.*, 1971), and the changes in renal tubule sodium concentration are such as to suppress rather than facilitate renin release (Gill and Casper, 1971).

A single dose of 20 mg practolol was found to reduce isoprenaline tachycardia by 50-60% at rates of infusion corresponding to approximately, 1, 2, and 3 μg per minute. Similar results have been reported by Brick *et al.* (1968).
In the present study, the drug was given in a single dose, rather than by the cumulative-dose technique which is sometimes used. The half-time of practolol in man is 8-12 hours (Fitzgerald and Scales, 1968). Since as Brick et al. (1968) had shown that the inhibition of isoprenaline-induced tachycardia by practolol was not related to dose in the range 5-20 mg, the single-dose technique was felt to adequately serve the aims of the study, which was to relate the effect of practolol on isoprenaline-induced renin release to the inhibition of the response in heart rate.

Unlike propranol, which lowers PRA at rest, and abolishes the rise in PRA produced by exogenous (Ayers et al., 1969) and endogenously released catecholamines (Assaykeen et al., 1970), practolol was found to be without effect on PRA. PRA at rest, and the elevation in PRA produced by isoprenaline, were not influenced by the drug. From studies on the renin response to tilting (Michelakis and McAllister, 1972) and hypoglycaemia (Assaykeen et al., 1970), there is good evidence that β-adrenergic mechanisms mediate in renin release, at least with these stimuli. As catecholamines have been shown to be capable, in vitro, of causing renin release (Michelakis et al., 1969), and the effect of isoprenaline appears to be a direct one, it could be speculated that the failure of practolol to inhibit renin release produced by isoprenaline, and the ability of propranolol to suppress secretion in this setting, point to specific β₂-adrenoceptor mediation in the direct release of renin.

The evidence however is insufficient to sustain this argument. Although practolol has much less activity than
propranolol against $\beta_2$-adrenoceptors (Barrett, 1971), this is not the only major difference between the 2 drugs. For example, the $\beta_1$-adrenoceptor blocking activity of the 2 drugs is not identical; the effect of practolol on the heart is largely chronotropic, compared with the inotropic and chronotropic effects of propranolol (Finegan et al., 1972). Further, the whole question of whether the release of renin by sympathetic nervous system stimulation or sympathomimetic amines is explicable in terms of classical receptor theory has been thrown open by the work of Winer et al. (1969, 1971). Findings of this group include blockade of the renin response to isoprenaline with phentolamine, suppression of the response to noradrenaline (predominant $\alpha$-agonist activity) with propranolol, and abolition of the renin response to isoprenaline by $d$-propranolol. Cyclic AMP has been shown by these workers to stimulate renin secretion, this response being suppressed by both $\alpha$- and $\beta$-adrenergic blocking drugs (Winer et al., 1971). These observations have been interpreted, not by reference to specific membrane receptors at cell surfaces, but rather in terms of intracellular actions of these agents distal to the generation of cyclic AMP. The longer half-life of practolol, and the fact that the majority of the drug is excreted unchanged in the urine, have been related to it having a lower lipid solubility than propranolol (Barrett, 1971). Reduced lipid solubility would perhaps prevent practolol from having an intracellular action on renin secretion such as that suggested for propranolol.

Whatever the basis of these anomalous findings, a failure of practolol to acutely inhibit renin release has
been observed. This finding supports the contention that decreased renin responsiveness with long-term oral dosage of practolol (Chapter 5) is secondary to reduced sympathetic nervous responsiveness.
### TABLE 6-1

**RESPONSES TO PRACTOLOL**

<table>
<thead>
<tr>
<th></th>
<th>Systolic BP mmHg</th>
<th>Diastolic BP mmHg</th>
<th>Heart Rate per min</th>
<th>Plasma Renin Activity ng/ml/hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before Practolol</td>
<td>103 ± 4</td>
<td>57 ± 6</td>
<td>57 ± 5</td>
<td>0.67 ± 0.26</td>
</tr>
<tr>
<td>Practolol 20 mg</td>
<td>106 ± 8</td>
<td>58 ± 8</td>
<td>56 ± 7</td>
<td>0.62 ± 0.21</td>
</tr>
</tbody>
</table>

Systolic BP, diastolic BP, heart rate, and plasma renin activity (mean ± standard deviation) in 5 normal subjects before, and 60 minutes after the intravenous injection of 20 mg practolol.

The drug produced no significant change in BP, heart rate, or PRA.
### TABLE 6-2
EFFECT OF PRACTOLOL ON THE RESPONSE TO ISOPRENAライン

<table>
<thead>
<tr>
<th></th>
<th>PRE-INFUSION</th>
<th>ISOPRENAライン INFUSION</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PRA ng/ml/hr</td>
<td>Heart Rate/min</td>
</tr>
<tr>
<td>Isoprenaline</td>
<td>0.86±0.25</td>
<td>52±5</td>
</tr>
<tr>
<td>Practolol plus</td>
<td>0.62±0.21</td>
<td>56±7</td>
</tr>
<tr>
<td>Isoprenaline</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The effect of isoprenaline, 10, 20, and 30 ng/Kg/min, on heart rate and PRA, with and without a prior dose of practolol, 20 mg.

The significance levels of the changes from pre-infusion values (paired t-test) are indicated; * p < 0.05, ** p < 0.01.
Figure 6-1. The changes in pulse rate and plasma renin activity with isoprenaline in 5 normal subjects, and the effect of practolol, 20 mg, on these changes.
CHAPTER 7
HIGH CATECHOLAMINE ESSENTIAL HYPERTENSION:
CLINICAL AND PHYSIOLOGICAL CHARACTERISTICS

SUMMARY

Urinary catecholamine excretion has been measured in patients with sustained essential hypertension, borderline hypertension, secondary hypertension, and in subjects with normal blood pressure. The urinary noradrenaline level was elevated in approximately 25% of patients with sustained essential hypertension, but was normal in all patients with borderline hypertension and secondary hypertension. The relationship of elevated noradrenaline levels to certain physiological and clinical characteristics of essential hypertensives that might be related to increased catecholamine production has been investigated. Of the characteristics studied, plasma volume, the responsiveness of the sympathetic nervous system, renin-angiotensin status, indices of emotional stress, and "hyperkinetic circulatory state", all proved to be unrelated to basal noradrenaline excretion. Urinary noradrenaline was related only to the level of the blood pressure, being highest in patients with more severe hypertensive disease.
INTRODUCTION

The possible role of the sympathetic nervous system in the genesis of essential hypertension has been widely investigated. Increased excretion of catecholamines in the urine in a proportion of patients with essential hypertension was an early finding (von Euler et al., 1954) which has been confirmed in some (Nestel and Doyle, 1968; Goodall and Bogdonoff, 1961), but not all (Crout et al., 1961) studies. The recent development of highly sensitive assays for catecholamines has led to the demonstration of elevated levels in plasma also (De Quattro, 1972; Engelman et al., 1970). The significance of these higher levels in some hypertensives, and the underlying mechanism, remain uncertain, but studies by De Quattro (1971) with labelled noradrenaline precursor suggest that in these patients the release of noradrenaline is increased.

In recent years, attempts have been made to classify essential hypertension in terms of certain physiological and clinical characteristics. There have been reports of reduced plasma volume (Tarazi et al., 1968), low plasma renin activity (Jose and Kaplan, 1969), increased responsiveness of the sympathetic nervous system (Frohlich et al., 1967), and prominent cardiac symptoms in hypertensives with "hyperkinetic circulation" (Frohlich, 1971). Changes in catecholamine production, or altered responsiveness to secreted catecholamines, might theoretically be encountered with each of these. Plasma volume is reduced in phaeochromocytoma (Brunjes et al., 1960), and the secretion of renin and noradrenaline are related through a common response to salt depletion and
hypovolaemia (Vander, 1967). Increased catecholamine production might occur in stress hypertension (Graham, 1945) accompanying chronic anxiety, or reflect the increased responsiveness of the sympathetic nervous system to adrenergic stimuli that has been reported in a proportion of patients with essential hypertension (Frohlich et al., 1967). Cardiac symptoms in hypertensives with "hyperkinetic circulation" might result from increased cardiac sympathetic nerve activity, or from high levels of circulating catecholamines.

In the present study, urinary free noradrenaline and adrenaline excretion has been measured in 35 patients with sustained essential hypertension (including 2 with malignant hypertension), 15 patients with borderline hypertension, 32 subjects with normal blood pressure, and 8 patients with secondary hypertension. The relationship of urinary catecholamine excretion to plasma volume, emotional stress, symptoms of "hyperkinetic circulatory state", responsiveness of the sympathetic nervous system, and renin-angiotensin status, has been assessed.

PATIENTS AND METHODS

Essential Hypertensives

Fifty untreated patients were studied, 35 with sustained essential hypertension and 15 with borderline hypertension. Forty-one had never received treatment for the hypertension, while 9 had received some treatment in the past, though not in the preceding 12 months. The absence of recent treatment was related to the fact that all were either newly diagnosed, previously diagnosed
defaulters, or patients with borderline hypertension. The blood pressure elevation was designated sustained hypertension or borderline hypertension on the basis of average casual, or 'usual' blood pressures (Julius and Schork, 1971), as outlined in Chapter 3. Secondary hypertension was reasonably excluded by routine screening procedures including urine microscopy and culture, serum and 24-hour urinary sodium and potassium levels, endogenous creatinine clearance, urinary catecholamine excretion, and in most cases intravenous pyelography (intravenous pyelography was not carried out in 7 patients with borderline hypertension). Phaeochromocytoma was excluded by negative responses to tilting (Harrison et al., 1967) and glucagon (Lawrence, 1967) in those subjects in whom further testing was indicated on the basis of urinary catecholamine levels. None of the female hypertensives was taking oral contraceptive drugs. The severity of the hypertensive disease was graded according to the scale of Corcoran et al. (1954). In 30 hypertensive patients it was felt that estimation of the duration of hypertension was possible, with adequate documentation from previous frequent medical examinations related primarily to employment. Duration was dated from the time that elevated pressure was first noted. The clinical diagnosis of "hyperkinetic circulatory state" (Frohlich, 1971) was made in 11 patients with essential hypertension on the basis of significant discomfort related to unexplained recurrent cardiac irregularities and palpitations. In addition, some of these patients had an elevated resting pulse rate, and complained of tremor, anxiety and attacks of sweating.
Thyrotoxicosis was excluded in this group. From the pattern of symptoms, and electrocardiographic evidence in most cases, the basis of the cardiac symptoms appeared to be sinus tachycardia in 8 patients, supraventricular tachycardia in 2, and multiple ventricular extrasystoles in one.

Patients with Secondary Hypertension

Of the 8 patients with secondary hypertension, 4 had oral contraceptive-induced hypertension, 3 had renal hypertension, and one had Cushing's syndrome. None had received treatment for the hypertension. In those with contraceptive-induced hypertension a family history of hypertension was absent and blood pressures were normal before commencing contraceptive therapy, but rose soon afterwards. Pressures fell to normal limits within 12 months of stopping oral contraceptive therapy. Renal biopsy in the 3 patients with renal hypertension disclosed chronic nephritis in 2 and membranous glomerulonephritis in the third. A large adenoma of the right adrenal gland was found at operation in the subject with Cushing's syndrome.

Normal Subjects

The 32 normotensive subjects comprised 8 student volunteers, and 24 ambulant general medical patients drawn from a medical ward and its associated outpatient department. None of the patients was acutely ill, and most had been referred for diagnostic procedures.

Experimental Procedure

The investigation was performed on the essential hypertensive patients as outpatients (29 subjects), or
during the first 2 days of hospital admission (21 subjects), to minimize any effects of confinement and prolonged recumbency (Dietrick et al., 1948). Smoking was forbidden on the morning of the test. After an overnight fast, subjects were rested flat in a single-bed ward for 90 minutes prior to the commencement of the study, at the end of which they emptied their bladders. Then followed a 90-minute test period, during which patients were maintained recumbent. Drinking water was provided to ensure an adequate urine flow. Blood pressure was measured with a sphygmomanometer at 10-minute intervals, with disappearance of sound taken as the diastolic endpoint. Resting BP was calculated as the mean of the 3 lowest recordings. At the end of this period, blood was drawn for assay of serum creatinine and the subjects voided. The urine was acidified and frozen for future assay of urinary free catecholamines and creatinine. Urinary free noradrenaline and adrenaline were assayed in duplicate by a modification of the trihydroxyindole method (Crout, 1961) with differential fluorimetry using 2 sets of filters (von Euler and Lishajko, 1959). Internal standards were carried through the entire procedure. Urinary creatinine was measured by a modification of the alkaline picrate method (Edwards and Whyte, 1958), serum creatinine was measured by autoanalyzer. From the serum creatinine concentration and urinary creatinine excretion, endogenous creatinine clearance was calculated. Urinary noradrenaline and adrenaline excretion was adjusted for within-group differences in GFR, and for incomplete emptying of the bladder, as follows:
Adjusted catecholamine excretion (µg catecholamine/litre of plasma cleared of creatinine) = catecholamine excretion (µg/min)/GFR(litre/min). As with the commonly adopted convention of expressing urinary catecholamines simply in relation to the rate of excretion of creatinine, the assumption is made that adrenaline and noradrenaline excretion is a function only of plasma levels and filtration, renal tubular mechanisms having no role. This remains unproven in man, and the evidence from animal experimentation is conflicting (Rennick and Pryor, 1965; Overy et al., 1967). Formal clearance studies in man are needed to clarify this point, but until definitive information is available, the adjustment of catecholamine excretion rates for differences in GFR would seem a satisfactory compromise. In 32 normal subjects a close correlation was observed between creatinine clearance and urinary noradrenaline excretion; r = 0.67, p < 0.001. All hypertensives studied but one (with normal catecholamine excretion) had a creatinine clearance of more than 80 ml per minute, so that discrepancies are not likely to have arisen through this adjustment.

In 18 subjects (10 male essential hypertensives, 8 male normal subjects) plasma volume was measured on the morning of the test using Evans Blue.

Psychometric Testing

Questionnaire-based psychometric testing was performed on 46 of the 50 patients with essential hypertension (mean age 37 years). Questionnaires used were the I.P.A.T. Anxiety Scale Questionnaire (Cattell and Scheier, 1963), which provides a measure of free-floating or manifest
anxiety, and the Eysenck Personality Inventory, Form A (Eysenck and Eysenck, 1964) which measures 2 dimensions of personality, neuroticism-stability and extraversion-introversion. Scores were compared with those of a control group of 40 age-matched general medical patients (mean age 36 years).

**Sympathetic Nervous System Responsiveness**

The sympathetic nervous system responsiveness to head-up tilting was assessed in all patients with essential hypertension and in 11 subjects with normal blood pressure using the methods outlined in Chapter 3.

**Renin Responsiveness**

Plasma renin activity (PRA) was measured in all essential hypertensive and 12 normotensive subjects using the bioassay method of Skinner (1967). Blood was obtained for PRA twice: first, after the subjects had rested flat for 3 hours after an overnight fast, and again after 90 minutes of 25° head-up tilt.

**RESULTS**

**Urinary Catecholamine Excretion**

The urinary adrenaline level was similar in all 4 groups (Fig. 7-1) with a level of 0.08 ± 0.07 µg/l (mean ± standard deviation) in patients with sustained hypertension, 0.08 ± 0.05 µg/l in patients with borderline hypertension, 0.06 ± 0.03 µg/l in patients with secondary hypertension, and 0.07 ± 0.06 µg/l in subjects with normal blood pressure.

The urinary noradrenaline level of 0.29 ± 0.14 µg/l in patients with sustained hypertension (Fig. 7-1) was significantly higher than the value of 0.20 ± 0.09 µg/l.
obtained in patients with normal BP (students t-test, p < 0.01). Noradrenaline in patients with borderline hypertension, 0.22 ± 0.09 µg/l, and secondary hypertension, 0.15 ± 0.07 µg/l, did not differ significantly from that of the normal subjects. Within the normal group, urinary noradrenaline level was similar in the volunteer and patient groups. In 8 of 35 patients with sustained hypertension, noradrenaline level was elevated, with values in excess of 0.38 µg/l, corresponding to a noradrenaline level of more than 2 standard deviations above the mean value found in the normal subjects. In no patient with borderline hypertension was the noradrenaline level outside the normal range.

Total catecholamine level was 0.37 ± 0.18 µg/l in patients with sustained hypertension, 0.30 ± 0.07 µg/l in patients with borderline hypertension, 0.21 ± 0.11 µg/l in patients with secondary hypertension, and 0.27 ± 0.13 µg/l in the normal subjects. Total catecholamine level was higher in patients with sustained hypertension than in the normotensive group (p < 0.02) solely due to the higher noradrenaline level.

Relationship of Catecholamine Levels to Blood Pressure

Urinary adrenaline level and the level of systolic and diastolic blood pressure were not significantly correlated in either the normotensive or essential hypertensive group (Table 7-1). In patients with essential hypertension there was a significant direct correlation between noradrenaline level and diastolic blood pressure (r = 0.44, p < 0.01; Fig. 7-2) and between noradrenaline and systolic blood pressure (r = 0.50, p < 0.001).
In subjects with normal blood pressure, noradrenaline level was significantly correlated with diastolic blood pressure only \((r = 0.41, p < 0.05; \text{Table 7-1})\). Urinary noradrenaline and the severity index of the hypertensive disease showed a positive correlation \((r = 0.39, p < 0.01; \text{Fig. 7-3})\). There was no correlation between duration of the hypertension and noradrenaline level.

**Plasma Volume**

Noradrenaline level and plasma volume were unrelated in the 18 male subjects in whom plasma volume was measured \((r = -0.06, \text{N.S., Fig. 7-4})\). Plasma volume was within normal limits in the 2 male essential hypertensives with elevated urinary noradrenaline.

**Personality Testing**

The I.P.A.T. Anxiety Scores in essential hypertensives and the control group of 40 medical inpatients were similar, 28.6 ± 12.9 compared with 31.0 ± 13.9. In the hypertensive group there was no correlation between noradrenaline level and anxiety score. In the 8 patients with high urinary noradrenaline, the anxiety score was 26.2 ± 12.4, similar to the overall scores for hypertensive and control subjects.

The Eysenck neuroticism score of 10.1 ± 5.2 in essential hypertensives was not significantly different from that in the control group, 11.1 ± 5.4. Neuroticism score and noradrenaline level were unrelated, and the score of 10.8 ± 5.5 in the hypertensives with high noradrenaline levels was within normal limits.

Adrenaline excretion also was unrelated to the anxiety and neuroticism scores.
Sympathetic Nervous System Responsiveness

In response to 25° head-up tilt, in 11 normal subjects the increase in diastolic BP was 5.1 ± 3.4 mmHg, and in urinary noradrenaline excretion, 0.05 ± 0.05 μg/l. Fourteen of 50 patients with essential hypertension who showed a rise in diastolic BP of 11 mmHg or more, or an increase in urinary noradrenaline greater than 0.15 μg/l, in response to tilting, have been defined as "sympathetic hyperresponders" on the basis of rises in diastolic BP or noradrenaline above the range of responses observed in the normal subjects. In 9 of these 14, both blood pressure and noradrenaline responses were above the normal range. Only one of these 14 subjects with an enhanced sympathetic response to posture had an elevated resting noradrenaline level. In fact, response to tilting was higher in borderline and mild sustained hypertension than in severe hypertension, although overall the negative correlation between severity index and noradrenaline response was of low order and not significant at the 5% level \( r = -0.28, \ 0.1 > p > 0.05; \) Fig. 7-3). The resting noradrenaline level, in contrast, was higher in severe hypertension (Fig. 7-3).

Renin Responsiveness

Plasma renin activity (PRA) during recumbency was 1.25 ± 0.78 ng/ml/hour in essential hypertensives (excluding 2 subjects with malignant hypertension) and 1.14 ± 0.38 ng/ml/hour in normal subjects. There was no correlation between urinary noradrenaline excretion and PRA level at rest in either group. PRA in 7 subjects with elevated noradrenaline levels (excluding one with malignant hypertension) was 0.94 ± 0.46 ng/ml/hour, which was similar to
the overall mean in essential hypertension. PRA with tilting was $1.48 \pm 0.41$ ng/ml/hour in normotensives. Six of the essential hypertensives, with a PRA of less than $0.66$ ng/ml/hour after 90 minutes of $25^\circ$ head-up tilt, had a renin level more than 2 standard deviations below the mean PRA during tilting in the normal subjects, and were categorized as "low renin essential hypertensives". Resting noradrenaline level in these subjects was $0.25 \pm 0.14$ µg/l, a value not significantly different from the overall mean in hypertensives, $0.27 \pm 0.13$ µg/l.

**Hyperkinetic Circulatory State**

In the 11 patients with unexplained recurrent palpitations in whom the clinical categorization of "hyperkinetic circulation" was made, noradrenaline level was $0.23 \pm 0.07$ µg/l and adrenaline level was $0.08 \pm 0.06$ µg/l. These values were similar to the overall means in hypertensives, $0.27 \pm 0.13$ µg/l for noradrenaline and $0.08 \pm 0.06$ µg/l for adrenaline.

**DISCUSSION**

The previous finding of an increased excretion of catecholamines in the urine in a proportion of patients with essential hypertension has been confirmed in this study. The increase was confined to an elevated noradrenaline level in approximately 25% of patients with sustained essential hypertension, adrenaline excretion not differing from that in subjects with normal blood pressure. Adrenaline and noradrenaline levels were normal in patients with borderline hypertension. Adjusted mean total catecholamine level, expressed in relation to GFR in
essential hypertensives was 0.35 μg/l (μg/l of catecholamines excreted per litre of plasma cleared of creatinine), and in subjects with normal BP was 0.27 μg/l. These figures compare with mean plasma total catecholamine levels of 0.35 μg/l in essential hypertension and 0.27 μg/l in normal subjects recently reported by De Quattro (1972) using the sensitive plasma catecholamine assay of Engelman et al. (1968), suggesting that adrenaline and noradrenaline may in fact be excreted passively by the kidney in man, and not subjected to the renal tubular mechanisms of secretion and reabsorption described in some other species (Rennick and Pryor, 1965; Overy et al., 1967).

It has been suggested that the higher catecholamine excretion in a proportion of patients with essential hypertension might be a reflection of chronic emotional stress (De Quattro, 1971). Questionnaire-derived levels of anxiety and neuroticism were within normal limits in the patients with high urinary noradrenaline excretion. That the higher catecholamine level is not a stress-induced phenomenon has not been entirely disproved as the psychological testing employed was directed at only a segment of total personality. However, if the hypertension is stress-related, it is not due to the interaction of stress with neurosis, nor is the stress-reaction manifest as a detectable anxiety state.

A proportion of patients with essential hypertension have a low plasma volume (Tarazi et al., 1968). Enhanced responsiveness of the sympathetic nervous system to adrenergic stimuli such as head-up tilting can be demonstrated in approximately one quarter of essential
hypertensives (Fröhlich et al., 1967). Speculation that high catecholamine levels in essential hypertension might be the result of a noradrenergic response to hypovolaemia, or reflect enhanced responsiveness of the sympathetic nervous system, has not been confirmed. The resting urinary noradrenaline level proved to be related neither to plasma volume nor to the responsiveness of the sympathetic nervous system to change in posture.

Low-renin essential hypertension appeared to be unrelated to the pattern of catecholamine excretion. It was anticipated but not confirmed that noradrenaline levels might in fact be low in low renin hypertension, in which increased total body exchangeable sodium has been demonstrated (Woods et al., 1969), as urinary catecholamine excretion is known to be related to sodium status, being highest in the presence of sodium depletion (Gordon et al., 1967). Our results differ from those of Crane et al. (1972), who have recently reported low total urinary catecholamine levels in low renin essential hypertension.

It was of interest that although cardiac sympathetic nerves are thought to contribute significantly to total catecholamine production and excretion (De Quattro and Sjoerdsma, 1968), adrenaline and noradrenaline levels in hypertensives with "hyperkinetic circulatory state" were similar to the overall mean figures for hypertensives. This suggests that the symptoms may possibly arise from overresponsiveness to normal levels of catecholamines.
such as has been suggested by Fröhlich et al. (1969) in hypertensives with "hyperdynamic β-adrenergic disease".

Of the clinical and physiological characteristics studied, the noradrenaline level proved to be related only to the level of the blood-pressure and to the severity of the hypertensive disease, subjects with severe hypertension having the highest noradrenaline levels. Although the release and excretion of noradrenaline is increased in essential hypertensives with high urinary catecholamine excretion (De Quattro, 1971), it seems unlikely that the modest elevations in noradrenaline levels observed in the present study could be the basis of large blood pressure elevations above the norm. However, the estimation of urinary catecholamines is an insensitive index of sympathetic nervous activity, and circulating and urinary levels of noradrenaline may incompletely reflect the concentrations of neurotransmitter at sympathetic nerve endings.

An increase in catecholamine levels secondary to sustained elevation of the blood pressure is a possible explanation for which there is no supporting evidence. Catecholamine levels may be elevated in congestive cardiac failure (Chidsey et al., 1962), but none of our patients had any evidence of congestive failure. The mean noradrenaline level in patients with sustained secondary hypertension did not differ significantly from the urinary noradrenaline level in subjects with normal blood pressure, in contrast to the elevated mean noradrenaline level in patients with sustained essential hypertension, perhaps supporting a primary role for the noradrenaline elevation
in the aetiology of essential hypertension. But interpretation of the lower noradrenaline level in these patients with secondary hypertension is difficult in view of the likelihood that there is sodium retention in these disorders.
TABLE 7-1
The Relationship of Urinary Adrenaline and Noradrenaline Excretion to Blood Pressure

<table>
<thead>
<tr>
<th></th>
<th>Systolic BP</th>
<th>Diastolic BP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Normal Subjects</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adrenaline</td>
<td>$r = + 0.13, \text{NS}$</td>
<td>$r = + 0.32, \text{NS}$</td>
</tr>
<tr>
<td>Noradrenaline</td>
<td>$r = + 0.26, \text{NS}$</td>
<td>$r = + 0.41, p &lt; 0.05$</td>
</tr>
<tr>
<td><strong>Essential Hypertension</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Borderline + sustained)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adrenaline</td>
<td>$r = + 0.18, \text{NS}$</td>
<td>$r = + 0.13, \text{NS}$</td>
</tr>
<tr>
<td>Noradrenaline</td>
<td>$r = + 0.50, p &lt; 0.001$</td>
<td>$r = 0.44, p &lt; 0.01$</td>
</tr>
</tbody>
</table>
Figure 7-1. Urinary adrenaline and noradrenaline levels in patients with sustained essential hypertension, borderline hypertension, secondary hypertension, and in subjects with normal BP. Mean values and standard deviations are indicated.
Figure 7-2. The relationship between resting diastolic blood pressure and urinary noradrenaline level. For patients with essential hypertension (borderline and sustained), $r = +0.44$, $p < 0.01$. 
Figure 7-3. Resting urinary noradrenaline levels, and the increase with $25^\circ$ head-up tilt, in patients with borderline hypertension (B), and in 3 grades of sustained hypertension (Grade I = Severity Index $< 2.5$, II = Severity Index 2.5 - 5.0, III = Severity Index $> 5.0$). Mean values and standard deviations are indicated.
Figure 7-4. The relationship between plasma volume and urinary noradrenaline level in 10 male hypertensive subjects and 8 male subjects with normal BP. Overall, $r = -0.06$, N.S.
CHAPTER 8

ANXIETY NEUROSIS AND INCREASED SYMPATHETIC NERVOUS ACTIVITY IN ESSENTIAL HYPERTENSIVES WITH SYMPTOMS OF HYPERKINETIC CIRCULATION

SUMMARY

In a consecutive series of 54 patients with untreated essential hypertension, 14 patients had symptoms of hyperkinetic circulation including frequent tachycardia, palpitations, sweating and anxiety which suggested a possible diagnosis of phaeochromocytoma. Studies were carried out to determine whether these symptoms reflected intrinsic overactivity of the sympathetic nervous system which might be causally related to the hypertension or whether they were manifestations of anxiety. In one subgroup of 6 subjects, psychometric testing indicated the symptoms were related to coexistent anxiety neurosis. A further 6 subjects, with normal levels of measured anxiety and neuroticism, demonstrated a high resting pulse rate, elevated plasma renin activity, and increased responsiveness of the sympathetic nervous system to orthostatic stress. Whether the increased sympathetic nervous activity observed in this group is related causally to the cardiac symptoms and the hypertension remains uncertain.
INTRODUCTION

Episodic palpitations, sweating, and tremor are symptoms common in phaeochromocytoma, and should suggest the diagnosis in any patient with hypertension. But the majority of hypertensive patients with such symptoms, when adequately investigated, prove not to have a catecholamine-secreting tumour. Significant discomfort related to recurrent cardiac irregularities, or rapid, forceful cardiac action, occurring without an obvious precipitant, or in relation to exercise or emotion, is a common complaint in these patients (Frohlich, 1971). Findings reported in these hypertensives with "hyperkinetic circulation" include an elevated resting pulse rate and cardiac output (Frohlich et al., 1969), enhanced responsiveness of the sympathetic nervous system and renin-angiotensin system to adrenergic stimulation (Kuchel et al., 1970), and increased sensitivity of the ß-adrenergic receptors of the heart to infused isoprenaline, in hypertensives with "hyperdynamic ß-adrenergic disease" (Frohlich et al., 1969).

That hypertension with hyperkinetic circulation constitutes a distinct subgroup of essential hypertension is open to question. Elevated cardiac output, high resting pulse rate, and increased responsiveness of the sympathetic nervous system have been reported in borderline and mild sustained essential hypertension, in the absence of cardiac symptoms (Eich et al., 1962; Frohlich et al., 1967). Further, it is well known that essential hypertension is commonly asymptomatic at the time of diagnosis, symptoms developing later in relation to anxieties induced by knowledge of the diagnosis and possible complications of
hypertension (Pickering, 1972). The symptoms described in hyperkinetic circulation are, in fact, non-specific, and similar to those found in neurocirculatory asthenia and anxiety states (Hurst and Logue, 1966).

The aim of the present investigation was to study the prevalence of symptoms of hyperkinetic circulation in a consecutive series of patients with untreated essential hypertension, and to investigate the relationship of these symptoms to levels of anxiety and neuroticism, and to the responsiveness of the sympathetic nervous system to adrenergic stimulation.

PATIENTS AND METHODS

Essential Hypertensives

54 untreated patients were studied, 39 with sustained essential hypertension and 15 with borderline hypertension. The blood pressure elevation was designated sustained hypertension or borderline hypertension on the basis of average casual, or "usual" blood pressure (Chapter 3). Resting urinary catecholamine levels and sympathetic and renin responsiveness of most of these patients has been described, in another context, in earlier Chapters.

45 patients had never received treatment for the hypertension, while 9 had received some treatment in the past, though not in the preceding 12 months. The absence of recent treatment was related to the fact that all were either newly diagnosed, previously diagnosed defaulters, or patients with borderline hypertension. Secondary hypertension was reasonably excluded by routine screening procedures including urine microscopy and culture, serum and 24-hour urinary sodium and potassium levels, endogenous creatinine clearance,
urinary catecholamine excretion, and in most cases intravenous pyelography (intravenous pyelography was not carried out in 7 patients with borderline hypertension). Phaeochromocytoma was excluded by negative responses to tilting (Harrison et al., 1967) and glucagon (Lawrence, 1967) in those subjects in whom further testing seemed indicated. None of the female hypertensives was taking oral contraceptive drugs.

The clinical diagnosis of "hyperkinetic circulatory state" (Frohlich et al., 1969; Frohlich, 1971) was made in 14 of these patients with essential hypertension. These patients all had significant discomfort related to unexplained recurrent cardiac irregularities, or rapid, forceful cardiac action, occurring without an obvious precipitant, or in relation to exercise or emotion. In addition, some of these patients had an elevated resting pulse rate, and complained of tremor, anxiety, and attacks of sweating. Thyrotoxicosis was excluded in this group.

Subjects with Normal BP

Two groups of normotensive subjects were studied. A consecutive series of 40 general medical patients from a medical ward and its associated outpatient department served as the control group for the psychometric studies. A second series of 32 normotensive subjects, comprising 8 student volunteers and 24 ambulant general medical patients, were the control group for the physiological studies. None of the patients in this second group was acutely ill, and most had been referred for diagnostic procedures.
Experimental Procedure

Urinary catecholamine excretion and plasma renin activity during recumbent rest, and the responsiveness of the sympathetic nervous system and renin-angiotensin system to change in posture, were measured.

Resting Plasma Renin Activity and Urinary Catecholamine Levels

The investigation was performed on all hypertensive subjects, 33 as outpatients, and 21 as inpatients, during the first 2 days of hospital admission, and on 32 normotensive subjects. Smoking was forbidden on the morning of the test. After an overnight fast, subjects were rested supine in a single-bed ward for 90 minutes prior to the commencement of the study, at the end of which they emptied their bladders. Then followed a 90-minute test period, the subjects remaining recumbent. Drinking water was provided to ensure an adequate urine flow. At the end of this period, blood was drawn for assay of plasma renin activity (i.e. after 3 hours of recumbency), and serum creatinine, and the subjects voided. The urine was acidified and frozen for future assay of catecholamines and creatinine.

Sympathetic Nervous System Responsiveness

Sympathetic nervous system responsiveness to head-up tilt was assessed in all patients with essential hypertension, and in 11 subjects with normal blood pressure, by the methods used in Chapter 3. The resting urinary catecholamine level during recumbent rest, and the responses
in diastolic blood pressure, pulse rate, urinary noradrenaline, and glomerular filtration rate to 90 minutes of 25° head-up tilt were measured.

**Renin Responsiveness**

Plasma renin activity (PRA) was measured in all hypertensive and 11 normotensive subjects using the bioassay method of Skinner (1967). All patients had been maintained on an unrestricted diet. Blood was obtained for PRA twice: first, after the subjects had rested flat for 3 hours after an overnight fast, and again after 90 minutes of 25° head-up tilt.

**Laboratory methods**

Urinary free noradrenaline and adrenaline were assayed in duplicate by a modification of the trihydroxyindole method (Crout, 1961) with differential fluorimetry using 2 sets of filters (von Euler and Lishajko, 1959). Internal standards were carried through the entire procedure. Urinary creatinine was measured by a modification of the alkaline picrate method (Edwards and Whyte, 1958), serum creatinine was measured by autoanalyzer. From the serum creatinine concentration and urinary creatinine excretion, endogenous creatinine clearance was calculated. Urinary noradrenaline and adrenaline excretion was adjusted for within-group differences in GFR, and for incomplete emptying of the bladder, as follows:

\[
\text{Adjusted catecholamine excretion (µg catecholamine/ litre of plasma cleared of creatinine)} = \frac{\text{catecholamine excretion (µg/min)}}{\text{GFR (litre/min)}}.
\]
Psychometric Testing

Questionnaire-based psychometric testing was performed on 50 of the 54 patients with essential hypertension, and on the control group of 40 general medical patients with normal blood pressures. Questionnaires used were the I.P.A.T. Anxiety Scale Questionnaire (Cattell and Scheier, 1963), and the Eysenck Personality Inventory, Form A (Eysenck and Eysenck, 1964).

RESULTS

The 14 hypertensives with hyperkinetic circulation appeared to fall into 3 distinct groups (Table 8-1). In six patients a diagnosis of anxiety neurosis could confidently be made. These subjects, all with anxiety scores of greater than 38 and neuroticism scores of greater than 14, had scores one standard deviation or more above the mean neuroticism and anxiety levels obtaining for the general population (Cattell and Scheier, 1963; Eysenck and Eysenck, 1964). In 2 patients cardiac stimulation seemed to be caused by exogenous pharmacological stimulation of the heart (Table 8-1). In one, it became apparent that symptoms were related to sinus tachycardia following the drinking of red wine. Symptoms occurred in no other context, and attacks were abolished when he stopped drinking. In the other, multiple ventricular extrasystoles seemed to be associated with a heavy consumption of coffee and tobacco. Symptoms and extrasystoles ceased when the patient stopped drinking coffee and smoking. The remaining 6 patients with hyperkinetic circulation, grouped purely on the basis
of exclusion of other apparent causes, have been categorized as "sympathetic hyperresponders" (Table 8-1), for reasons to be described.

**Hypertensives with Hyperkinetic Circulation and Anxiety Neurosis**

The anxiety score in this group was $50 \pm 3$ (mean $\pm$ standard deviation), and the neuroticism score was $18 \pm 2$ (Table 8-1). Anxiety and neuroticism levels were significantly higher than the levels in both the control group of general medical patients, $31 \pm 14$ and $11.1 \pm 5.4$, $p < 0.01$, and the hypertensive subjects without cardiac symptoms, $27 \pm 13$ and $9 \pm 5$, $p < 0.001$. The scores in these hypertensives with anxiety neurosis compare with scores of 46 for anxiety and 14.4 for neuroticism reported in 2 groups of patients, with a clinically significant anxiety state (Cattell and Scheier, 1963) and mixed neurosis (Eysenck and Eysenck, 1964). 4 of these 6 patients had sustained hypertension, including 2 with hypertensive retinal changes and electrocardiographic evidence of left ventricular hypertrophy, making it unlikely that the elevation in blood pressure was simply a manifestation of an anxiety state. Sinus tachycardia, often with an emotional precipitant, was the basis of cardiac symptoms in all (Table 8-1). Associated symptoms such as sweating, anxiety, and tremor were common. In this group, the urinary catecholamine levels, resting pulse rate, and the sympathetic responsiveness to head-up tilt were within normal limits (Tables 8-2 and 8-3).
Sympathetic Hyperresponders

The 6 hypertensives with hyperkinetic circulation, without anxiety neurosis of drug-induced cardiac stimulation as an apparent cause of their symptoms, were categorized as "sympathetic hyperresponders". The basis of cardiac symptoms was paroxysmal supraventricular tachycardia in 3, sinus tachycardia in 2, and multiple ventricular extrasystoles in one. Anxiety and neuroticism levels were within normal limits (Table 8-1), but associated symptoms of sweating, tremor, and anxiety were frequently noted, so that the clinical presentation of this group, apart from the higher incidence of supraventricular tachycardia, was similar to that of the patients with symptoms of hyperkinetic circulation and anxiety neurosis. Additional findings were an elevated resting pulse rate (71 ± 9 per minute compared with 63 ± 7 in the subjects with normal blood pressure, \( p < 0.05 \); Table 8-2), high PRA (2.69 ± 1.18 ng/ml/hr compared with 1.09 ± 0.40, \( p < 0.001 \); Table 8-2), and an enhanced sympathetic responsiveness to head-up tilt (Table 8-3). The changes in diastolic BP, urinary noradrenaline, and glomerular filtration rate with tilting were all greater than those in the subjects with normal BP (\( p < 0.001 \), Table 8-3). The increase in PRA with tilting, 0.56 ± 0.16 ng/ml/hr, was marginally greater than that in the control subjects, 0.33 ± 0.24, but the difference was not significant at the 5% level (0.1 > \( p > 0.05 \)).

Compared with the hypertensive patients without cardiac symptoms, this group had a higher PRA at rest (\( p < 0.001 \)), and with tilting, larger rises in diastolic blood pressure.
(p < 0.001), pulse rate (p < 0.05), noradrenaline level (p < 0.01), and PRA (p < 0.05), and a greater reduction in glomerular filtration rate (p < 0.01) (Tables 8-2 and 8-3).

**Hypertensives without Cardiac Symptoms**

In these patients, the only difference from the findings in the subjects with normal BP was a higher resting urinary noradrenaline level, 0.28 ± 0.13 µg/l compared with 0.20 ± 0.09, p < 0.01.

**Relationship of Onset of Symptoms to Time of Diagnosis of Hypertension**

The mean time elapsed since diagnosis of the hypertension was similar in patients with and without cardiac symptoms, 4.3 years compared with 4.4 years (Table 8-1). In all hypertensives with anxiety neurosis and cardiac symptoms, symptoms preceded the diagnosis of hypertension. Overall among the hypertensives with hyperkinetic circulation, 10 of 14 had cardiac symptoms prior to the diagnosis of hypertension.

**DISCUSSION**

Although symptoms of episodic palpitations, sweating and anxiety in patients with an elevated blood pressure should suggest the possible diagnosis of phaeochromocytoma, most hypertensive patients with these symptoms do not have a catecholamine-producing tumour. Over the period of observation of the present study, 16 patients referred for work-up of hypertension presented symptoms of hyperkinetic circulation. 14 of these patients had essential
hypertension, in a total of 54 patients finally diagnosed as having essential hypertension, and have been described. Of the remaining 2 patients, one had thyrotoxicosis, and the other was the only case of phaeochromocytoma in the series.

The term "hyperkinetic circulation" has found wide usage in the literature on essential hypertension, but the meaning remains ill-defined and confusing. Symptomatology, physical findings, and haemodynamic findings have been used to differing extents by different authors in categorizing the syndrome. An elevated resting pulse rate, elevated cardiac output, and cardiac symptoms have all been emphasized (Julius et al., 1971; Frohlich, 1971). The limits of the syndrome are not well defined, and the relationship of hypertension with "hyperkinetic circulation" to "neurocirculatory asthenia" (Hurst and Logue, 1966) and to the "hyperkinetic heart syndrome" (Gorlin, 1962) for example, is not clear. In the present study, the diagnosis of "hyperkinetic circulation" was made on the basis of the pattern of cardiac and associated symptoms. Cardiac outputs were not measured.

Essential hypertensives with hyperkinetic circulation were found not to constitute a homogeneous group. Excluding 2 subjects in whom cardiac symptoms seemed to be provoked by extrinsic pharmacological stimulation, by red wine in one and coffee and nicotine in the other, the patients with hyperkinetic circulation fell into 2 groups. In the first, with symptoms very similar to those of neurocirculatory asthenia, the presence of anxiety neurosis
was demonstrated. The psychological disorder was presumably the basis of the symptoms. In all of these patients with anxiety neurosis, symptoms had preceded the diagnosis of the hypertension, and were not a result of anxieties raised by knowledge of the diagnosis and possible complications of hypertension. The elevated blood pressure recorded was not a temporary BP elevation accompanying an anxiety state, as 4 of the 6 patients in this category had retinal or electrocardiographic stigmata of hypertensive disease. The role of chronic anxiety in the aetiology of essential hypertension is an unsolved question (Gutman and Benson, 1971); the presence of both anxiety neurosis and essential hypertension in these patients may well have represented the coexistence of 2 common, unrelated disorders. The concept of a "hypertensive personality" is difficult to support on current evidence (Gutmann and Benson, 1971).

In the second group of hypertensives with hyperkinetic circulation, no evidence of psychological abnormality was disclosed by the methods of testing used. These patients differed from the group with anxiety neurosis in having an elevated resting pulse rate, high plasma renin activity at rest, increased responsiveness of the sympathetic nervous system to change in posture, and by the occurrence of paroxysmal supraventricular tachycardia (in 3 of 6 subjects). Adrenergic overactivity has been presumed to underly the symptoms and haemodynamic changes of hyperkinetic circulation (Frohlich, 1971). An increased responsiveness of the sympathetic nervous system to one stimulus, that of change in posture, has been demonstrated in a proportion
of our patients. Whether increased responsiveness to other adrenergic stimuli exists in these patients is not known. Greater than normal increases in adrenaline and noradrenaline excretion have been reported in borderline hypertensives exposed to mental stress (Nestel, 1969). Cardiac sympathetic nerves are thought to contribute significantly to total noradrenaline production and excretion (De Quattro and Sjoerdsma, 1968). The high noradrenaline response to change in posture in the hypertensives with sympathetic hyperresponsiveness suggests increased cardiac sympathetic nerve activity as the possible basis of the symptoms, especially since cardiac symptoms in hypertensives with hyperkinetic circulation are said to be commonly posture-related (Fröhlich et al., 1969).

The basis of the higher plasma renin activity at rest, a finding previously reported in patients with hyperkinetic circulation by Kuchel et al. (1970) is not clear. The higher PRA may possibly be related to the increased sympathetic nervous responsiveness, as the sympathetic nervous system has been shown to play an important role in renin release (Vander, 1967). However this interpretation is not supported by the finding that the PRA response to tilting was only marginally higher in the sympathetic hyperresponders than in the subjects with normal blood pressure.

Noradrenaline excretion under resting conditions was significantly higher in the hypertensives without cardiac symptoms than in the subjects with normal BP. An
elevated urinary excretion of noradrenaline at rest, in a proportion of patients with essential hypertension, has been observed in several studies (von Euler et al., 1954; Nestel and Doyle, 1968). These patients tend to be the ones with the more severe hypertensive disease (Chapter 7). In this study, the hypertensive patients without cardiac symptoms had the highest mean severity index, higher than in the 2 groups of hypertensives with hyperkinetic circulation. The higher noradrenaline excretion at rest in the group of hypertensives without cardiac symptoms was presumably related to the disproportionately large number of patients with severe hypertensive disease it included.

A group of essential hypertensive patients with symptoms of hyperkinetic circulation, raised heart rate, increased sympathetic nervous responsiveness, and high plasma renin activity has been delineated. Whether this is in any sense an aetiologically distinct and separate subgroup of essential hypertension is not known.
<table>
<thead>
<tr>
<th>Diagnostic Category</th>
<th>No. of Subjects</th>
<th>Mean Age (years)</th>
<th>Ratio of Borderline to Sustained Hypertension</th>
<th>Psychometrics</th>
<th>&quot;Usual&quot; Basis of Palpitations BP (mmHg)</th>
<th>Severity Index</th>
<th>Duration of Symptoms (years)</th>
<th>Time Elapsed Since Diagnosis of Hypertension (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertensives with Hyperkinetic Circulation:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety Neurosis</td>
<td>6</td>
<td>31</td>
<td>1:2</td>
<td>50 ± 3**</td>
<td>18 ± 2** Sinus tachycardia in all.</td>
<td>1.5 ± 1.4</td>
<td>10 ± 5.4</td>
<td>2.3 ± 1.7</td>
</tr>
<tr>
<td>Extrinsic Cardiac Stimulation</td>
<td>2</td>
<td>36</td>
<td>-</td>
<td>26</td>
<td>14 Sinus tachycardia in one, multiple ventricular extrasystoles in one.</td>
<td>3.0</td>
<td>3</td>
<td>1.5</td>
</tr>
<tr>
<td>Sympathetic Hyperresponders</td>
<td>6</td>
<td>35</td>
<td>1:2</td>
<td>20 ± 6</td>
<td>7.8 ± 3 Supraventricular tachycardia 3, sinus tachycardia 2, ventricular extrasystoles one.</td>
<td>1.1 ± 0.7</td>
<td>6.8 ± 2.8</td>
<td>7.2 ± 6.3</td>
</tr>
<tr>
<td>Hypertensives without Cardiac Symptoms</td>
<td>40</td>
<td>38</td>
<td>1:2.1</td>
<td>27 ± 13</td>
<td>9 ± 5 170/105</td>
<td></td>
<td>2.3 ± 2.6</td>
<td></td>
</tr>
<tr>
<td>Subjects with Normal Blood Pressure</td>
<td>40</td>
<td>36</td>
<td>-</td>
<td>31 ± 14</td>
<td>11.1 ± 5.4 121/76</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Means and standard deviations are listed. Asterisks refer to significance level (student's t-test) of the difference between values in subjects with normal BP and those in each hypertensive subgroup: **p < 0.01.
<table>
<thead>
<tr>
<th>Diagnostic Category</th>
<th>No. of Subjects</th>
<th>Urinary Catecholamine Levels (µg/l)</th>
<th>Pulse Rate (per min)</th>
<th>Plasma Renin Activity (ng/ml/hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertensives with Hyperkinetic Circulation:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety Neurosis</td>
<td>6</td>
<td>0.22 ± 0.05</td>
<td>0.09 ± 0.04</td>
<td>67 ± 9</td>
</tr>
<tr>
<td>Sympathetic Hyperresponders</td>
<td>6</td>
<td>0.22 ± 0.08</td>
<td>0.05 ± 0.04</td>
<td>71 ± 9*</td>
</tr>
<tr>
<td>Hypertensives without Cardiac Symptoms</td>
<td>40</td>
<td>0.28 ± 0.13**</td>
<td>0.08 ± 0.06</td>
<td>64 ± 10</td>
</tr>
<tr>
<td>Subjects with Normal Blood Pressure</td>
<td>32</td>
<td>0.20 ± 0.09</td>
<td>0.07 ± 0.06</td>
<td>63 ± 7</td>
</tr>
</tbody>
</table>

Means and standard deviations are listed.

Asterisks refer to significance level (student's t-test) of the difference between values in subjects with normal BP, and those in the hypertensive subgroups; *p < 0.05, **p < 0.01, ***p < 0.001.
<table>
<thead>
<tr>
<th>Diagnostic Category</th>
<th>No. of Subjects</th>
<th>Change in Diastolic BP (mmHg)</th>
<th>Change in Pulse Rate (per min)</th>
<th>Change in Urinary Noradrenaline (µg/l)</th>
<th>Change in GFR (%)</th>
<th>Change in Plasma Renin Activity (ng/ml/hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertensives with Hyperkinetic Circulation:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety Neurosis</td>
<td>6</td>
<td>+3.8 ± 5.7</td>
<td>+9.7 ± 4.7</td>
<td>+0.09 ± 0.07</td>
<td>-16 ± 10</td>
<td>+0.44 ± 0.06</td>
</tr>
<tr>
<td>Sympathetic Hyperresponders</td>
<td>6</td>
<td>+14 ± 3.2**</td>
<td>+14 ± 5</td>
<td>+0.22 ± 0.08***</td>
<td>-39 ± 10***</td>
<td>+0.56 ± 0.16</td>
</tr>
<tr>
<td>Hypertensive without Cardiac Symptoms</td>
<td>40</td>
<td>+4.5 ± 6.4</td>
<td>+8.4 ± 5.0</td>
<td>+0.07 ± 0.11</td>
<td>-8 ± 17</td>
<td>+0.25 ± 0.31</td>
</tr>
<tr>
<td>Subjects with Normal Blood Pressure</td>
<td>11</td>
<td>+5.1 ± 3.4</td>
<td>+9.5 ± 6.3</td>
<td>+0.05 ± 0.05</td>
<td>-7.7 ± 13.7</td>
<td>+0.33 ± 0.24</td>
</tr>
</tbody>
</table>

Means and standard deviations are listed.

Asterisks refer to significance level (Student's t-test) of the difference between responses in subjects with normal BP and those in each hypertensive subgroup; ***, p < 0.001.
CHAPTER 9

INTERPRETATION AND CONCLUSIONS

In this thesis, resting and reflex activity of the sympathetic nervous system has been studied particularly with respect to the pathogenesis of hypertension. The release of renin and the antihypertensive activity of the β-adrenergic blocking drug, practolol, have been studied from the point of view of their relationship to the reflex activity of the sympathetic system. Sympathetic nervous system responsiveness has been assessed by studying the changes in blood pressure, urinary noradrenaline excretion, and glomerular filtration rate elicited by stimuli such as changing posture. Quantitative interrelationships have been observed between the increments in diastolic BP and urinary noradrenaline, and the fall in GFR with head-up tilting (Chapter 3). The mean responses in the hypertensive group studied were similar to those in subjects with normal blood pressure. Some hypertensives, however, were underresponsive to tilting, with small changes in diastolic BP, noradrenaline level and GFR, while approximately one quarter of essential hypertensives, categorized as "orthostatic hyperresponders", had larger rises in diastolic pressure and noradrenaline and a larger fall in GFR with tilting than occurred in the normotensive subjects. When these hyperresponders were retested, a high degree of reproducibility could be demonstrated over an interval of up to 2 years (Chapter 3). This is similar to the experience of Frohlich et al. (1967).
1. **Hyperresponsiveness to Tilt.**

The clinical correlates of sympathetic responsiveness to tilting have been outlined in Chapter 3. An inverse relationship was noted between responsiveness to tilting and both the severity and the duration of the hypertension. As a group, the tilt hyperresponders had borderline or mild sustained hypertension, and tended to be young, with recent onset of the hypertension. Six of 14 had symptoms of hyperkinetic circulation (Chapter 8).

The basic mechanism underlying an enhanced response is not known. The published work on baroreceptor sensitivity in essential hypertension provides no evidence to suggest that the increased reflex responsiveness could arise at this level: baroreceptor sensitivity is if anything reduced in mild hypertension (Bristow *et al.*, 1969). The possibility of disturbed function at other levels, such as in relation to the central integration of sympathetic function, or involving the nerve terminals, has not been investigated. These tilt hyperresponders do not have a generalized sympatho-adrenomedullary overresponsiveness to adrenergic stimulation. Their catecholamine responses to the other stimuli tested, hypoglycaemia and "mental stress", were within normal limits (Chapter 4). As adrenergic overresponsiveness was therefore confined to change in posture, the possibility was entertained that the enhanced sympathetic responsiveness to upright posture was directly related to the pathogenesis of the hypertension, rather than merely reflecting a generalized sympathetic overresponsiveness. Some findings reported in this thesis support this contention, but the evidence is indirect and incomplete.
The first line of evidence relates to the possibility that there may be a posture-related retention of sodium in the tilt hyperresponders. These patients had larger falls in glomerular filtration rate and larger rises in plasma renin activity with tilting than subjects with normal BP (Chapter 3, Chapter 4), providing a potential mechanism for sodium retention and elevation of blood pressure. Sodium-loading in sensitive animals, such as the partially nephrectomized dog (Coleman and Guyton, 1969), leads to an elevation in cardiac output and arterial pressure. Fröhlich and associates (1967) have reported cardiac output to be higher in orthostatic overresponders than in hypertensives with a normal or reduced response to tilt. The acute effects of tilting on urinary sodium excretion, however, were not in accord with this line of reasoning: the mean reduction in urinary sodium excretion with tilting was no greater in tilt hyperresponders than in normally reacting hypertensives (Chapter 4).

A second line of evidence suggesting that an enhanced sympathetic response to upright posture may be the mechanism by which a sustained elevation of the BP is produced in some hypertensive patients derives from studies with the β-adrenergic blocking drug, practolol (Chapter 5). This drug proved to be an effective antihypertensive agent in the majority of patients in doses of up to 800 mg daily. However at low doses, the BP was lowered significantly more in the tilt hyperresponders than in other hypertensives. In the orthostatic overresponders, the fall in BP to normal levels with practolol was associated with a reduction in the sympathetic response to tilt, also to within normal limits.
Both these lines of evidence are very indirect. The enhanced response to tilting in some hypertensives may well reflect only increased sympathetic nervous activity which is secondary to other, possibly more important factors, such as altered renin-angiotensin status (Chapter 4).

2. The Effect of Practolol on Sympathetic and Renin Responsiveness.

The β-adrenergic blocking drug, practolol, has been evaluated as an antihypertensive agent in patients with essential hypertension (Chapter 5). As indicated, the blood pressure fall produced by a low dose of the drug proved to be related to the previously assessed level of sympathetic nervous system responsiveness to tilting. When the responses to tilt were retested during practolol therapy, they were found to be reduced. In the tilt hyperresponders, the responses were reduced to within normal limits by practolol, to return to pretreatment levels when the drug was stopped. The renin response to tilting was also reduced in patients taking practolol, although the resting level of PRA was not significantly changed. Practolol seems to have no direct effect on renin release (Chapter 6). As a close relationship existed between the sympathetic and renin response to tilt in untreated hypertensive patients (Chapter 4), it is likely that the reduced renin response noted with practolol therapy reflected the diminished reflex sympathetic activity in patients taking the drug, rather than resulting from a direct effect of practolol on renin release.
The predominant mechanism by which β-adrenergic blocking drugs lower BP is not known. Although a fall in cardiac output occurs with long-term oral dosage of β-blockers (Frohlich et al., 1968), this does not appear to be the major antihypertensive mechanism (Tarazi and Dustan, 1972). A reduction in reflex sympathetic and renin responsiveness with practolol has been reported here. While it is not clear whether this could lead to a sustained lowering of blood pressure in essential hypertension, it does represent a possible mode of action for these drugs.


In Chapter 4, a positive correlation between the responses in urinary noradrenaline and plasma renin activity to head-up tilting was reported in patients with essential hypertension. This is consistent with the known role of the sympathetic nervous system in mediating renin release (Vander, 1967). "Tilt hyperresponders" had a greater renin response than either normotensive subjects or other hypertensives. A corollary finding was that sympathetic responsiveness to tilting was reduced in patients with low-renin essential hypertension.

Hypertensive patients with a small sympathetic and renin response to tilting appeared to fall into 2 categories. One group, the low-renin hypertensives, had low PRA at rest, and a small renin response to tilt. In the second group, PRA at rest was within normal limits, but sympathetic and renin responses to tilt were diminished. Sympathetic responsiveness to tilting was related to the severity of the hypertensive disease (Chapter 3). By and large, the
members of this second group, with a normal PRA level at rest, had severe hypertensive disease. Of the 6 patients with low resting PRA, 5 had borderline or mild sustained hypertension only. Sympathetic underresponsiveness was therefore found in 2 situations: firstly, in patients with severe hypertensive disease, together with a reduced renin response to tilt, but normal PRA at rest, and secondly, in patients with low-renin hypertension, in whom PRA was reduced both in response to tilt and at rest. In the low-renin hypertensives, the findings could possibly be related to an increased total body sodium content, since PRA at rest, and sympathetic and renin responsiveness to the upright posture are all reduced in primary aldosteronism (Biglieri et al., 1962).

4. "High Noradrenaline Essential Hypertension".

The previous finding of an increased excretion of catecholamines in the urine in a proportion of patients with essential hypertension (von Euler et al., 1954; Nestel and Doyle, 1968) has been confirmed (Chapter 7). The increase was confined to an elevated noradrenaline level in approximately 25% of patients with sustained hypertension. Noradrenaline excretion at rest was normal in patients with borderline hypertension. No relationship was observed between resting noradrenaline excretion and certain physiological and clinical characteristics of essential hypertensives that might be related to increased catecholamine production, such as plasma volume, reflex sympathetic activity, renin-angiotensin status, and levels of anxiety. Urinary noradrenaline excretion was related only to the
level of the blood pressure, being highest in patients with more severe hypertensive disease.

Total peripheral vascular resistance is also elevated in patients with more severe hypertension (Bello et al., 1967). A neurogenic basis for the elevated TPR in these patients with severe disease would be the simplest interpretation of the finding of increased noradrenaline excretion.
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