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INTRODUCTION

It is of considerable interest to review the historical development of the drug treatment of hypertension. It is now a little over 30 years since Paton and Zaimis[1] described the pharmacological activities of a new class of substances, the polymethylene bistrimethylammonium salts. Two of the series, the C5 and C6 compounds were shown to have powerful and selective blocking properties on transmission through autonomic ganglia, acting by competitive inhibition of the neurotransmitter acetyl-choline. Most of the early clinical studies using these substances to treat hypertension were disappointing because the absorption of these substances from the alimentary tract was variable and the drugs caused severe postural hypotension. However, one study undertaken by Sir Horace Smirk[2] in New Zealand made use of a complicated regimen of parenteral administration of these substances with very careful adjustment of the dose to induce a controlled postural hypotension with the systolic blood pressure falling to about 120–140 mmHg when the patient stood erect. Complex though this regime was, the results of treatment were dramatic. The fundal changes of malignant hypertension resolved, the hypertensive heart failure was relieved in almost all patients, and there was a reduction in the incidence of stroke.

These results were of particular importance because they indicated that many of the manifestations of hypertension were due to the elevated blood pressure itself and that lowering this to normal or near normal levels, could reverse or abolish the pathological effects. Although this idea seems self evident now, the view was widely held at that time that the high blood pressure was a response to some other factor and that reducing the blood pressure would lead to irreversible ischaemia or to other disadvantages. Perhaps for this reason, the era preceding the development of ganglion blocking drugs was one of therapeutic nihilism with a few exceptions. However, the use of the low salt diets had been shown earlier to produce dramatic amelioration of many of the manifestations of hypertension and this has led to a vogue for bilateral adrenal surgery which was considerably less successful. The other major line of treatment was bilateral thoraco-lumbar sympathectomy but the extensive nature of this operation excluded all but a few patients from being suitable for it. Thus the demonstration by Smirk continued and effective blood pressure reduction produced improvement in many of the manifestations of hypertension was a very significant finding indeed.

One of the major disadvantages of the ganglion blocking drugs was the extensive nature of their side effects. These drugs which blocked not only sympathetic ganglia and so reduced blood pressure, but also para-sympathetic ganglia, caused severe side effects such as dryness of the mouth, constipation, failure of accommodation of the eye, impotence and retention of hearing. Although in Smirk's regime the side effects were minimized by the accuracy of the dosage, and the incompleteness of the ganglion blockade, they were, nevertheless, troublesome. It was the need to overcome these side effects which was one of the main stimuli to the development of the multiple drug approach to hypertension which was pioneered by Schroeder who used a combination of hydrallazine and hexamethonium the so-called Hyphex Regime. Smirk and his colleagues showed that side effects due to the ganglion blockers were greatly minimized if Reserpine was added to the ganglion blockers and with the development of oral diuretics during the late 1950's, it became evident that combinations of drugs could be used with the effect of reducing the doses of individual drugs and hence the side effects of each.

The demonstration that reduction of blood pressure had a favourable therapeutic result was one of the major causative factors in the widespread search for new and novel antihypertensive agents. The earliest regime was sufficiently complex and unpleasant to restrict its practical use to those patients with the severest manifestation of hypertension. New antihypertensive drugs began to appear in the 1960's with the introduction firstly of

selective adrenolytic drugs such as guanethidine, or bethanidine, later with the introduction of alpha methyldopa and later still clonidine and the beta adrenoreceptor blocking drugs. At the same time as the search for new antihypertensive agents developed, there was in parallel a major development in the understanding of pathophysiological mechanisms of hypertension. The sodium retaining hormone aldosterone was isolated in the mid-1950's and was followed shortly afterwards by the description of primary aldosteronism, while the relationship between the renin angiotensin system and aldosterone became widely recognised is the 1960's. The introduction of clonidine and the recognition of the central action of methyldopa led to a resurgence in interest in the central mechanism of blood pressure control. It is fair to say that a great deal of the understanding of the pathophysiology of hypertension has been the result of, rather than the stimulus to, the development of new antihypertensive drugs. Nevertheless, it is clear that an understanding of the pathophysiological mechanisms of hypertension is desirable for the understanding of the clinical pharmacology of antihypertensive drugs, a fact which is reflected in the various chapters in this volume.

From the earliest development of antihypertensive drug treatment there has been controversy as to which hypertensive patients should be treated. In general, the more unpleasant or dangerous the drugs available the more severe does hypertension need to be before treatment could be justified. The important studies by the Veterans Administration[3,4] of the effects of treatment of mild and severe hypertension, provided a further impetus to antihypertensive treatment. The Veterans Administration Study of severe hypertension made it clear that all patients with severe hypertension require treatment and the results of the study in milder hypertensives, although inconclusive, suggested that these patients also might benefit. More recently, the results of the High Blood Pressure Detection Follow-up Programme in the United States[5] and of the Australian Therapeutic Trial in Mild Hypertension[6], have indicated clearly that even patients with mild or borderline hypertension, benefit from antihypertensive drug treatment, those patients treated experiencing both reduction in mortality and a reduction in cardiovascular complications as compared to those subjects taking placebos. Thus in 30 years the scope of antihypertensive drug treatment has widened from having a limited application in those patients with severe and life threatening disease to a preventive medicine programme in which as many as 20% of the population may be considered to derive benefit from such treatment.

The present volume has a major emphasis on pathophysiological mechanisms of hypertension and relates the clinical pharmacological and therapeutic aspects to these.

The volume contains sections on the renin angiotensin system, the autonomic nervous system, the role of sodium in hypertension, aldosterone in hypertension and an over-view of the various pathophysiological mechanisms. The problem of malignant hypertension is sufficiently important to justify a separate chapter on both mechanisms and management. Finally, the volume contains on clinical aspects of hypertension, the beta adrenoreceptor blocking drugs, the dilemma of mild hypertension and the results of treatment. It is hoped that the volume will contribute to the understanding of hypertension and hypertensive vascular disease and thus contribute to the better management of patients with this disorder.

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CONTENTS

CHAPTER 1

PATHOPHYSIOLOGICAL MECHANISMS IN ESSENTIAL HYPERTENSION

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1. INTRODUCTION

Although a great variety of factors can produce elevation of blood pressure, they can only do so by increasing either cardiac performance or vascular resistance or both. The determination of the haemodynamic setting therefore, should take precedence over any other analysis of potential mechanisms in the elaboration of high blood pressure (Fig. 1). This paper is therefore primarily concerned with the haemodynamic and fluid volume states of essential hypertension. This will then be followed by a discussion of potential underlying mechanisms.

2. HAEMODYNAMICS AND BODY FLUID VOLUMES

2.1. SYSTEMIC HAEMODYNAMICS

An elevated peripheral resistance together with a normal or subnormal cardiac output has been considered to be the prevalent pattern in essential hypertension for many years (Wiggers, 1938; Goldring and Chasis, 1944; Bolomey *et al.*, 1949; Werkö and Lagerlöff, 1949).

A variant finding has been obtained in young subjects with borderline or labile hypertension, in that cardiac output can be markedly increased (Varnauskas, 1955; Widimski *et al.*, 1958; Brod, 1960; Fejfar and Widimski, 1961; Rowe *et al.*, 1961; Eich *et al.*, 1962, 1966; Bello *et al.*, 1965, 1967; Finkielman *et al.*, 1965; Sannerstedt, 1966; Lund-Johansen, 1967; Kioschos *et al.*, 1967; Frohlich *et al.*, 1969, 1970; Safar *et al.*, 1970, 1973; Julius *et al.*, 1971*a*; Ellis and Julius, 1973; Tarazi *et al.*, 1974; Miura *et al.*, 1978). Although

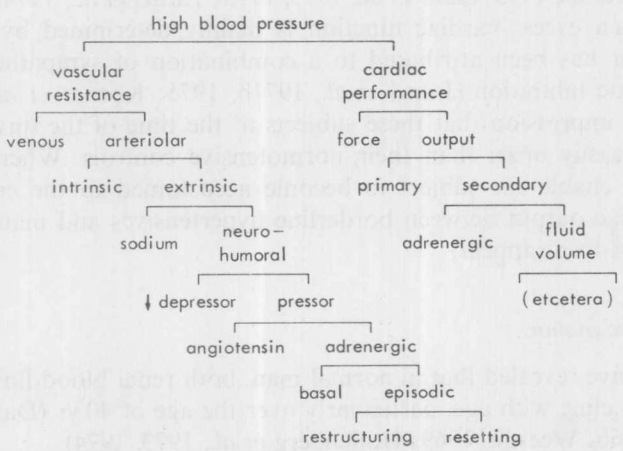

FIG. 1. Approach of the prevailing mechanism in essential hypertension. The diagram shows that each set of options logically follows from the preceding decision, however arbitrary that may be. The primary decision should be based on haemodynamic data, since the resultant derivatives for the greater part are fundamentally different.

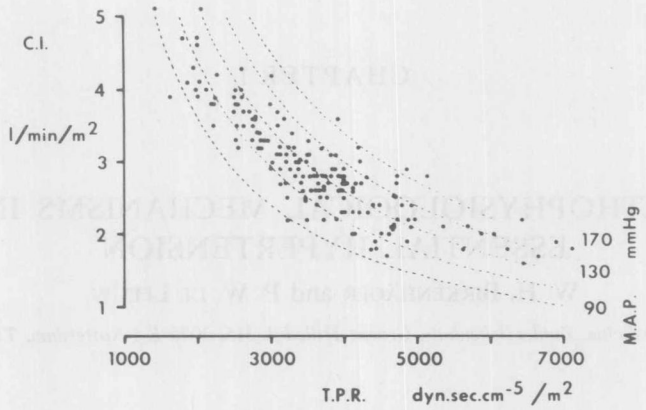

FIG. 2. The balance between cardiac index (C.I.) and (derived) total peripheral vascular resistance (T.P.R.) and the resultant arterial pressure in the authors' series of essential hypertensives. The distribution across the isobaric lines is slightly skewed, in that the contribution of vascular resistance tends to increase with increasing severity of hypertension.

peripheral resistance seems to be normal as a numerical value, it is actually increased or at least not adjusted when the data are compared with those of a control population (Julius *et al.*, 1971; Birkenhäger and Schalekamp, 1976).

The balance between cardiac output and vascular resistance in the authors' series is presented in Fig. 2. It is apparent that the higher the blood pressure, the lower the contribution of cardiac index.

More or less corresponding to the different haemodynamic accents, hypertensives have been roughly classified in two groups: one with labile or mild hypertension and one with fixed hypertension. Although in the final analysis only a minority of patients with labile (borderline) hypertension (30 per cent) show an increased cardiac output, it has been stated that this condition is a precondition for the future development of hypertension. Epidemiologic studies revealed a higher incidence of sustained hypertension in patients with a previously hyperkinetic circulation (Levy *et al.*, 1944, 1945). However, borderline hypertension *per se* is already a fairly good predictor of future established hypertension (Julius and Schork, 1971) and it cannot be assumed that this is due solely to the hyperkinetic circulation, since that only occurs in part of this population. In most studies, the high cardiac output state could be attributed to an increase in heart rate (Eich *et al.*, 1962; Sannerstedt, 1966; Lund-Johansen, 1967; Julius and Schork, 1971; Julius *et al.*, 1971a,b; Ellis and Julius, 1973; Safar *et al.*, 1973, 1975; Tarazi *et al.*, 1974), stroke volume being normal. When excess cardiac function is mainly determined by heart rate, the underlying disorder has been attributed to a combination of sympathetic overactivity and parasympathetic inhibition (Julius *et al.*, 1971b, 1975; Korner *et al.*, 1973). In our studies, we got the impression that these subjects at the time of the (invasive) measurements were more easily upset than their normotensive controls. When we adopted a policy designed to enable the subject to become accustomed to the environment, the differences in cardiac output between borderline hypertensives and matched normotensive controls tended to disappear.

2.1.1. *Renal Haemodynamics*

Several studies have revealed that in normal man, both renal blood flow and glomerular filtration rate decline with age, particularly over the age of 40 yr (Davies and Shock, 1950; Lee *et al.*, 1966; Weeson, 1969; Hollenberg *et al.*, 1973, 1974).

Glomerular filtration rate is maintained for a longer period than renal plasma flow; this means that the filtration fraction (F.F.) which is defined as the quotient of G.F.R. and R.P.F. has a tendency to rise with age.

Although renal blood flow is sometimes normal in essential hypertension (Goldring and Chasis, 1944; Pedersen and Kornerup, 1976; Pedersen, 1977), in the majority of patients renal perfusion appears to be diminished (Friedman *et al.*, 1941; Hilden, 1948; Bolomey *et al.*, 1949; Pfeiffer *et al.*, 1950; Bello *et al.*, 1960; Brod *et al.*, 1962; Ladefoged, 1968; Hollenberg *et al.*, 1969). When G.F.R. was measured, it was found to be within normal limits in most studies. Thus, filtration fraction and renal vascular resistance tend to be increased in essential hypertension. In our studies we observed a negative relationship of renal blood flow with respect to age. In our hypertensive population the average reduction per decade was 68 ml/min. When our results are compared to those of Wesson (1969), the decrease in renal plasma flow appears steeper for the hypertensives. Similarly, Safar *et al.* (1976a) found a negative relation between renal blood flow and age in hypertensives aged 20–40 yr but not in age-matched normotensives. An increase in renal vascular resistance is apparent even at an early stage of the disease. With hypertension of longer duration, as reflected by age, there is a steep increase in renal vascular resistance.

2.1.2. *Intrarenal Haemodynamics*

The kidney is a structurally heterogeneous organ: a distinction can be made between superficial (outer cortical) and deep (corticomedullary) glomeruli. They seem to have both a different function and blood supply. The normal cortex is perfused at a flow rate of about 300–500 ml/min/100 g (Rosen *et al.*, 1968; Ladefoged and Pedersen, 1969; Hollenberg, 1968, 1969, 1970; Blaufox *et al.*, 1970; Kew *et al.*, 1971; Kilcoyne *et al.*, 1973; Kolsters, 1976).

Several authors have reported a diminished cortical flow in hypertensive patients (Ladefoged and Pedersen, 1969; Hollenberg *et al.*, 1968; Dell *et al.*, 1973; Kilcoyne *et al.*, 1973; Logan *et al.*, 1973; Kolsters, 1976).

Cortical flow rate declines with advancing age both in normals (Hollenberg *et al.*, 1973, 1974a; Kolsters, 1976) and in hypertensives (Kolsters, 1976).

2.1.3. *Relations Between Renal and Systemic Haemodynamics*

In a few early studies, renal haemodynamics were found to be more depressed at higher levels of blood pressure (Moyer *et al.*, 1958; Möller, 1960; Heidland *et al.*, 1962). However, no regression analysis was carried out in these studies. Pedersen and Kornerup (1976) and Safar *et al.* (1976a) found significant inverse relations between renal blood flow and mean arterial pressure. This could be confirmed in our series (Fig. 3). The relation is independent of age. Hypertension *per se* has therefore, a considerable impact on the renal vasculature. Similar conclusions can be reached when the relation between

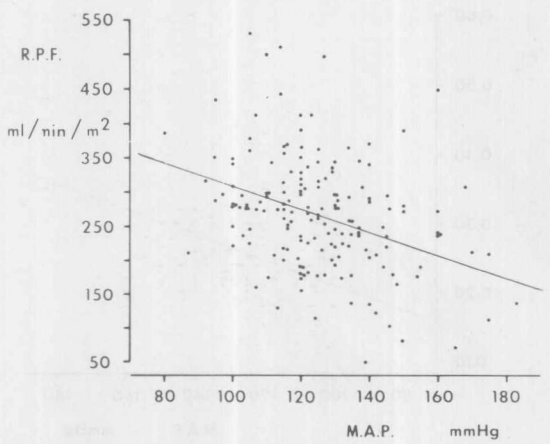

FIG. 3. Relationship between mean arterial pressure (M.A.P.) and renal plasma flow (R.P.F.) in the authors' series of essential hypertensives ($r = -0.39$; $p < 0.001$).

renal blood flow and cardiac output is considered. In earlier studies from our laboratory, a direct relationship was found between renal blood flow and cardiac output (Birkenhäger *et al.*, 1968, 1972a) and this has recently been confirmed in borderline hypertension (Messerli *et al.*, 1978). In our patients, the renal fraction of cardiac output decreases significantly with age. At the age of 20 yr, the expected renal fraction is about 20 per cent, which is similar to that which would be expected in normals (Lee *et al.*, 1966) and is reduced to about 16 per cent at the age of 70 yr. This implies that in normal subjects, renal vascular resistance rises in proportion to the rise in total vascular resistance, but in hypertension the rise in renal vascular resistance exceeds the rise in total resistance. Other studies in hypertensive patients have also revealed a lower renal fraction in comparison to normotensives, this being due to diminished renal blood flow rather than changes in cardiac output (Bolomey *et al.*, 1949; Taquini *et al.*, 1962; Brod, 1973; Kolsters, 1976).

These findings indicate that the kidney is preferentially affected by the hypertensive process. It is likely that, despite the raised resistance, the increased pressure is transmitted along the renal vessels, since renal venous wedge pressure is also elevated in hypertensive patients (Lowenstein *et al.*, 1970).

2.1.4. *Filtration Processes*

One of the intriguing features of essential hypertension is a steady increase in filtration fraction, the latter being directly related to the height of blood pressure (Fig. 4). This is due to the fact that glomerular filtration rate is less affected than renal plasma flow. In normotensives, glomerular filtration rate is well preserved until about 40 yr of age. Thereafter, it declines progressively, the average decrease, between 20 and 90 yr, being 46 per cent (Davies and Shock, 1950). Regression analysis showed the reduction to be about 1.0 ml/min/yr. In our hypertensive patients, the decline in filtration rate with age was less in comparison to the normotensives. From 20 to 70 yr of age, filtration rate declined only 25 per cent with an average reduction of 0.4 ml/min/yr. In a prospective study Reubi (1960) also showed that filtration rate does not decrease more rapidly with age in hypertensives than it does in normotensives.

2.2. BODY-FLUID VOLUMES

Several authors have emphasized the role of body fluid status in blood pressure control (Guyton, 1963; Guyton and Coleman, 1969; Guyton *et al.*, 1974; Coleman and Guyton, 1969; Tobian, 1972).

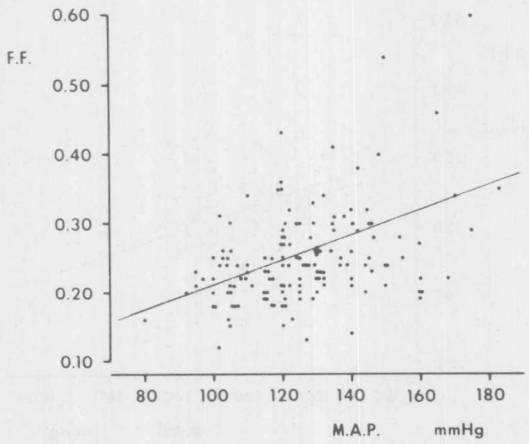

FIG. 4. Relationship between mean arterial pressure (M.A.P.) and filtration fraction (F.F.) in the authors' series of essential hypertensives ($r = 0.45$; $p < 0.001$).

In essential hypertension plasma volume or blood volume may be normal (Grollman and Shapiro, 1953; Cranston and Brown, 1963; Jones *et al.*, 1964; Bello *et al.*, 1965; Hansen, 1968; Ellis and Julius, 1973; Schalekamp *et al.*, 1974; Distler *et al.*, 1974; Weidmann *et al.*, 1977) or reduced (Rochlin *et al.*, 1960; Finkielman *et al.*, 1965; Tibblin *et al.*, 1966; Tarazi *et al.*, 1968, 1969, 1970; Julius *et al.*, 1971c; Molzahn *et al.*, 1972; Ibsen and Leth, 1973; Parving *et al.*, 1974; Dustan *et al.*, 1973; Safar *et al.*, 1973, 1976b; Ulrych, 1973). By pooling accessible data from several studies a slight but significant reduction of plasma volume in essential hypertension is observed (Fig. 5).

An inverse relationship between intravascular volume and blood pressure has been found in some studies (Tarazi *et al.*, 1968; Kuramoto *et al.*, 1968; Julius *et al.*, 1971c; Ulrych, 1973; Safar *et al.*, 1976) and denied in others (Tarazi *et al.*, 1970; Ibsen and Leth, 1973; Birkenhäger and Schalekamp, 1976; Weidmann *et al.*, 1977). In addition, an inverse relation between plasma or blood volume and total peripheral resistance has been reported (Bello *et al.*, 1965; Finkielman *et al.*, 1965; Taylor *et al.*, 1957; Birkenhäger *et al.*, 1968; Julius *et al.*, 1971c; Dustan *et al.*, 1973; Ulrych, 1973; Safar *et al.*, 1976; Chau *et al.*, 1978; Messerli *et al.*, 1978). Extracellular volume or total exchangeable sodium in hypertension have been found to be normal by some investigators (Walser *et al.*, 1956; De Graeff, 1957; Hollander *et al.*, 1961; Tarazi *et al.*, 1969; Novak *et al.*, 1972; Ibsen and Leth, 1973; Lebel *et al.*, 1974; Schalekamp *et al.*, 1974) and increased by others (Grollman and Shapiro, 1953; Teng *et al.*, 1954; Hansen, 1968).

The differences between the various studies probably can be attributed to patient selection, time of measurement, body weight and dietary regimen. A difference in plasma volume between males and females is generally recognized (Birkenhäger and Schalekamp, 1976).

2.3. The Haemodynamic Basis of Essential Hypertension

In the previous paragraphs we have attempted to analyze available data on separate haemodynamic and allied variables. The general haemodynamic pattern of essential hypertension appears to be one of a normovolaemic or slightly hypovolaemic state with an inappropriately high systemic vascular resistance as the common denominator. In addition, young subjects with labile hypertension tend to exhibit an elevated cardiac output. The haemodynamic situation at rest can be altered physiologically (exercise, change in posture, mental activity), experimentally (saline infusion) or pharmacologically (diuretics, anti-adrenergic agents). An overview of these provocative manoeuvres has been presented recently (Birkenhäger and Schalekamp, 1976).

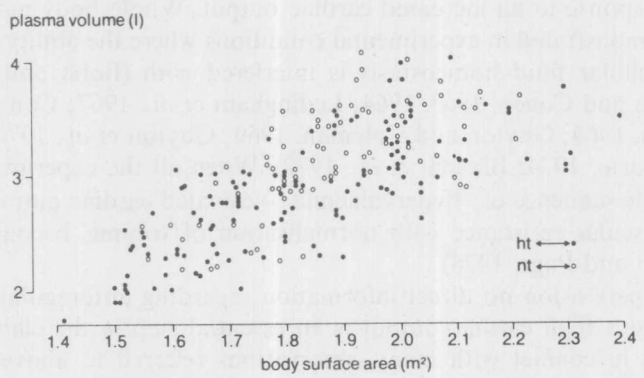

FIG. 5. Relationships between plasma volume and body surface area in 128 essential hypertensives (ht.) and as compared to those in 83 normotensives (nt.). There is a slight tendency for plasma volume to be reduced in hypertensives. These data were taken from several laboratories including our own. (From W. H. Birkenhäger and M.A.D.H. Schalekamp: Control Mechanisms in Essential Hypertension.)