THE SIXTH VOLHARD LECTURE

Causal and homoeostatic factors in hypertension

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Introduction

It is an honour and privilege to give this lecture to commemorate the great contributions made by Franz Volhard to hypertension research. Through outstanding clinical and pathological studies, Volhard and his collaborators separated what we now know as essential hypertension from the hypertension associated with nephritis and other types of parenchymal renal disease, and described malignant hypertension. Up till then these disorders had all been lumped together as complications of Bright's disease. Volhard's great monograph Die Doppelseitigen Haemato-
genen Nierenerkrankungen (Bright'sche Krank-
heit) [1] was published in 1918 and contains a wealth of material and hypotheses about the causes of hypertension. He speculated that the pale, sickly looking patient with renal disease, the 'blasse Hochdruckkranke', had a humoral factor constricting his arteries, and showed that this was not a catecholamine. In addition, he considered that primary arteriosclerotic changes of the renal arteries might be responsible for the hypertension in the well looking patient with essential hypertension, the 'rote Hochdruckkranke'.

The modern classification of hypertension into primary or essential hypertension, and secondary hypertension with known pathological causes [2], grew directly from the famous classification of Volhard & Fahr [3]. All types of established hypertension have, however, many features in common; for example, the adaptive hypertrophy of the heart and resistance vessels which Björn Folkow discussed in the Fourth Volhard Lecture [4]. Unfortunately we still know too little about the full sequence of steps in the pathogenesis of almost every type of secondary hypertension, even when we produce it ourselves in the laboratory. Such knowledge is important if we are ever to understand the bewildering array of abnormalities present in patients with fully developed essential hypertension.

In this lecture I want to first consider the haemodynamic patterns. Some types of hypertension begin with elevation of cardiac output and some with an elevated total peripheral resistance (TPR), but in longstanding hypertension it is mostly the rise in TPR that accounts for the elevated blood pressure. The amplification provided by the hypertrophied heart and vessels plays an important role in the changing patterns. Next, I want to consider the development of one-kidney 'benign' renovascular hypertension, where the hydraulic properties of the stenosis are crucial for the subsequent events. Here all the changes, apart from the stenosis, can be considered homoeostatic adjustments to maintain renal function. This includes the development of cardiovascular hypertrophy, which is a major factor contributing to the maintenance of established hypertension. Homoeostatic alterations in circulatory function also operate in established essential hypertension, where they greatly increase the difficulty of detecting possible primary cause(s) in individual patients. We have recently found that the vascular hypertrophy can be almost completely reversed after prolonged treatment and when the latter is stopped hypertension redevelops rapidly. This provides a possible new approach to the longitudinal or sequential analysis of essential hypertension, which may allow us to distinguish the initiating causes from the variety of 'homoeostatic' functional disturbances.

Many of the ideas on the development of hypertension would never have emerged without the help and stimulus of my collaborators in this work. I am particularly indebted to Drs W. Anderson, J. Angus, A. Bobik, A. Broughton, M. Esler, P. Dorward, P. Fletcher, G. Jennings, J. Oliver and M. West, who have worked with me over the last 6-10 years, mostly at the Baker Medical Research Institute.
Circulatory control system in hypertension

Blood pressure is the product of cardiac output and total peripheral resistance ($Q_s$ and TPR in Fig. 1). Chronic elevation of cardiac output may occur owing to (i) enhanced myocardial contractility, (ii) increased cardiac filling due to elevation of blood volume in relation to venous capacity; this may be caused by underlying renal or hormonal abnormalities which have been lumped together as ‘volume’ factors. Elevation of TPR may be due to (i) increased constrictor factors, e.g. increased sympathetic nerve activity, an increase in pressor hormones or reduction in dilator substances, (ii) altered contractility of vascular smooth muscle, e.g. through changes in electrolyte composition.

Whatever may be the initiating cause of hypertension the elevation of the blood pressure produces ‘work’ hypertrophy of the muscle of the heart and resistance vessels [4–6]. These become amplifiers of all inotropic and constrictor stimuli and as a result they make an increasing contribution to the maintenance of the elevated pressure. A corollary is that this amplification will tend to reduce the contribution of some of the homoeostatic factors present during the early stages of the hypertension through the normal operation of the control system in Fig. 1.

The neural control of blood pressure does not appear to be geared to operate about any fixed ‘set point’. Recently Coleridge et al. [7] and Dorward et al. [8] have shown that the threshold of the arterial baroreceptors themselves is reset within minutes of any sustained change in resting blood pressure. As a result the entire baroreceptor reflex appears to have a floating set point, with only a short 'memory' for any absolute level of blood pressure [8]. In addition central nervous system interactions involving arterial baroreceptors, cardiac baroreceptors, other peripheral afferents and central ‘command’ mechanisms are further mechanisms capable of producing rapid changes in reflex properties [9–11]. There is no evidence to suggest that the regional mechanisms involved in regulation of blood flow [12,13] have any longer memory for a particular absolute level of resting blood flow, as implied in the auto-regulation theory of hypertension, which is considered below.

Haemodynamic patterns

Human hypertension

Widimsky and colleagues [14] first observed that resting cardiac output was often elevated in young patients with essential hypertension and this has been confirmed by several other groups (for references see [15]). On average, these patients (including those with ‘borderline’ hypertension) have cardiac output values which are about 15% higher than in age-matched control
Sequential analysis of hypertension

FIG. 2. Haemodynamic findings in different groups of hypertensive patients: BH, young and borderline hypertension; EHI, established hypertension with minimum complications; EHII, established hypertension with some complications; AC, aortic coarctation; RVH, renovascular hypertension. Average mean arterial pressure (MAP) is given above each column; all other variables are expressed as percentages of age-matched control groups (for \( n \) of each group see Fig. 2 of [15]). (Based on [15].)

subjects, whilst TPR is relatively normal (Fig. 2: BH). By contrast, in uncomplicated essential hypertension cardiac output is normal and TPR is elevated (Fig. 2: EH I). Patients with longstanding untreated hypertension generally show some reduction in cardiac output and a rise in TPR; the increase in their output and stroke volume during exercise is also reduced [15, 16]. When the heart is enlarged cardiac output is often below that of age-matched control subjects and TPR is even higher (Fig. 2: EH II) [15].

Not all young patients with essential hypertension have a high cardiac output, but the range of output values (standard deviation in Fig. 2) is significantly greater than in established hypertension [15, 17–24]. One interpretation of this greater variance is that the young hypertensive subjects are a heterogeneous group, with diverse causes for the elevation of blood pressure. Another explanation was first suggested by Borst & Borst-de Geus [25]: that the elevated cardiac output was an early phase of essential hypertension and that the high TPR was a later development. This hypothesis has been extended and is now called the autoregulation theory of hypertension.

**Autoregulation theory of hypertension**

The theory postulates that the high cardiac output accounts for the initial elevation of the blood pressure and leads to perfusion of the tissues in excess of metabolic needs. The initial cardiac output-mediated rise in blood pressure is believed to trigger an increase in active tension of the vascular smooth muscle of the resistance vessels, through mechanisms that are similar to those involved in normal short-term autoregulation of peripheral blood flow [12]. This produces a ‘compensatory’ rise in TPR, which eventually restores cardiac output to a value close to the initial level.

Ledingham and associates [26, 27] and Guyton and colleagues [28–31] have been strong advocates of the autoregulation theory. Experimental support for it has come from studies on the effects of salt and fluid overload in patients and animals with gross renal impairment [30–32]. These showed an initial elevation of cardiac output, which was followed over a period of 7–14 days by a rise in TPR and restoration of cardiac output. However, not all studies in renal dialysis patients have observed such a haemodynamic transformation. McGrath et al. [33] maintained patients for 2 weeks each on 10 mmol and 100 mmol of sodium/day and found that over this range of salt loads the higher intake was associated with higher cardiac output but no change in TPR. There are numerous other studies on the development of experimental hypertension which are not in accord with the autoregulation theory (e.g. [27, 34–40]).

In my opinion there are at least three arguments against the autoregulation theory of
FIG. 3. (a) Average changes in cardiac output (CO), mean arterial pressure (MAP) and total peripheral resistance (TPR) on control days (C) and for 32 days after renal wrapping (ten rabbits) or sham-operation (nine rabbits) of the New Zealand white strain. Results are expressed as percentages of initial control values (data from [37]). (b) Average haemodynamic changes in ten sham-operated rabbits and ten rabbits with stable established renal wrap hypertension of the English multicoloured strain. Results are those obtained at the end of high salt (H), normal salt (N) and low salt (L) diets. CO, Cardiac output (ml/min); MAP, mean arterial pressure (mmHg); RAP, right atrial pressure (mmHg); TPR, total peripheral resistance (units); PCV, packed cell volume. * Significant change from value on normal salt (data from [14]).

From the salt and fluid overload studies, the time of transformation from high cardiac output to high TPR is 7–14 days, which is far greater than the time of 0.5–15 min involved in short-term regulation of peripheral blood flow and 'whole body' autoregulation of cardiac output [12, 13, 41]. This makes it most unlikely that the two processes have similar underlying mechanisms. (2) Hypertension is maintained through cardiac output changes alone for weeks in several types of experimental hypertension (see below). (3) The autoregulation theory does not explain how output ever falls below normal, as commonly occurs in longstanding hypertension in man (Fig. 2) [15, 16, 42] or in experimental animals [37, 43]. The theory implies that regulation is through an 'integral' type of control system with long memory for a previous level of blood flow, for which there is no evidence at present. An alternative hypothesis concerning the dominance of TPR in longstanding hypertension is considered later.

Two experiments from our laboratory suggest that TPR or cardiac output alone can each exert long-term effects on blood pressure. In the first experiment we studied the time course of haemodynamic changes during the first 32 days of development of bilateral renal cellophane wrap hypertension in rabbits on their normal laboratory diet [37] (Fig. 3a). Throughout the
experiment the mean arterial pressure (MAP) and TPR were higher in renal wrapped than sham-operated rabbits. The differences were significant from the beginning, but were small at first and increased with time. In both wrapped and sham-operated groups there were identical rises of 8–10% in cardiac output during the first week after operation. We therefore considered these changes to be a non-specific consequence of operation. We were fortunate that the disturbance of ‘volume’ factors affecting cardiac output were the same in both groups. We concluded that the hypertension was mediated entirely through a rise in TPR and that the early cardiac output changes were irrelevant to its development.

In the second experiment the confusion between constrictor and volume factors that had occurred in the early part of the first study was avoided by waiting 6 weeks after operation, when the rises in blood pressure and TPR had reached a plateau (Fig. 3b) [44]. We wished to know whether altering volume factors would alter blood pressure entirely through cardiac output, or whether TPR would also change. Six weeks after operation each renal wrapped and sham-operated rabbit was studied for 2 weeks on low, normal and high dietary salt intakes (approximately 0-5, 7, 30 mmol of sodium/day). In the sham-operated group these differences in salt intake produced no changes in MAP, cardiac output, TPR or blood volume (Fig. 3b). However, in the hypertensive rabbits on low sodium diet MAP was reduced by 12 mmHg below the levels on the other diets and this was entirely accounted for by reduction in cardiac output (Fig. 3b). TPR was the same after 2 weeks on each of the three diets, which is not in accord with the autoregulation theory.

Long-term changes in blood pressure entirely through changes in cardiac output have also been observed in haemodialysis patients during alterations in sodium intake [33], in ACTH hypertension in sheep [45] and in steroid hypertension in dogs [46]. In the last two types of hypertension blood pressure is entirely elevated through cardiac output alone at the beginning. In sheep this continues uniformly for several weeks (B. A. Scoggins, personal communication) and a similar response has been observed in about half the dogs [46].

Role of the cardiovascular amplifiers

Folkow and colleagues [4–6] first showed the importance of hypertrophy of the muscle of the heart and resistance vessels in amplifying inotropic and pressor stimuli. The vascular hypertrophy involves every organ bed [47]. In experimental renal hypertension the hypertrophy develops rapidly pari passu with the rise in pressure, reaching full development between 10 and 20 days after applying the clip [48]. We have examined the effects of hypertrophy in renal hypertensive animals studied during autonomic blockade to avoid secondary reflex effects [49–51]. We found that a given dose of noradrenaline, angiotensin II (ANG II) and vasopressin all produced greater rises in hindlimb vascular resistance in hypertensive than in normotensive rabbits (Fig. 4) [49, 51]. The enhancement was similar with all these drugs, suggesting a relatively non-specific effect (Table 1). The rise in hindlimb vascular resistance of hypertensive rabbits was about 1.9 times the responses of normotensive controls. The increased responsiveness in TPR of hypertensive rabbits was slightly smaller, about 1.6 times the responses of normal rabbits (Table 1). The increased reactivity is about the same in the rabbit hindlimb as in human limb vessels and in the resistance vessels of genetically hypertensive rats [4–6, 49, 51, 52].

In the dog with cardiac hypertrophy after 2–4 months of Goldblatt hypertension the effects of inotropic stimuli on contractile performance were assessed under conditions of controlled left atrial pressure [53]. In hypertensive dogs resting left ventricular (dP/dt)max was about 1.3 times that in matched controls and this difference was maintained right up to maximum inotropic stimulation with noradrenaline (Fig. 4a) (Table 1) [50]. This increase in contractile performance was proportional to the increased left ventricular mass. As a result the hypertrophied heart can maintain a given level of cardiac output at a higher blood pressure than the normal heart (Fig. 4a, insert).

### Table 1. Average slopes of pressor substance dose–response curves in autonomically blocked hypertensive rabbits and dogs expressed in relation to slope of matched normotensive group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Response to</th>
<th>Slope ratio (hypertension/normotension)</th>
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<tbody>
<tr>
<td>HVR</td>
<td>Noradrenaline</td>
<td>1.82</td>
</tr>
<tr>
<td></td>
<td>Angiotensin II</td>
<td>1.85</td>
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<tr>
<td></td>
<td>Vasopressin</td>
<td>2.00</td>
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<tr>
<td>TPR</td>
<td>Noradrenaline</td>
<td>1.60</td>
</tr>
<tr>
<td>LV(dP/dt)max</td>
<td>Noradrenaline</td>
<td>1.30</td>
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HVR, Hindlimb vascular resistance [49, 51]; TPR, total peripheral resistance (unpublished data); left ventricle (LV) (dP/dt)max was obtained at a left atrial pressure of 15 mmHg [50, 53].
In hypertension the hypertrophied heart and vessels have different haemodynamic amplyfying capacities, which determines why eventually blood pressure comes to be maintained by TPR whatever the initial haemodynamic pattern. Although the results in Table I came from different species, they suggest that in established hypertension amplification of \( \frac{dP}{dt} \), an index of myocardial tension \( [53] \), is less than that of vascular resistance. In the hypertrophied heart amplification of \( \frac{dP}{dt} \) is adequate to maintain normal levels of cardiac output at higher blood pressures, whereas the somewhat greater amplification provided by the vessels will produce accentuated rises in vascular resistance (Figs. 4 and 5). With continuing hypertrophy encroachment on the lumen will tend to increase still further the responses of the hypertrophied resistance vessels, but in the left ventricle it will eventually limit diastolic filling and stroke volume. Hypertrophied heart muscle probably also has greater problems with the supply of oxygen than hypertrophied vascular muscle, because of differences in fibre size and in the microcirculatory architecture \( [12, 47, 54] \). In hypertensive dogs lowering aortic diastolic pressure from 120 to 80 mmHg leads to significant falling off in resting \( \frac{dP}{dt} \) at constant left atrial pressure, but has no effect in normal dogs \( [50] \). Similarly, chronic tachycardia produced by sino-aortic denervation is less well tolerated in hypertensive rabbits than in normal rabbits and depletes their left ventricular catecholamines \( [55] \). This resembles the changes observed in chronic cardiac failure, though the hypertensive animals had no overt signs of this.
Sequential analysis of hypertension

In the early stages of hypertension the amplifying capacity of the heart and vessels will be evenly matched, so that hypertension can be maintained for long periods either through elevation of cardiac output alone or through TPR alone, depending on the initiating causes in the different experimental models.

When eventually cardiac hypertrophy no longer keeps pace with vascular hypertrophy, or if cardiac performance becomes depressed in some other way, TPR assumes greater prominence in the maintenance of hypertension. With continuing hypertension the heart may no longer be able to maintain cardiac output normal at the high arterial pressures (Fig. 4a, insert). The pattern of gradual reduction in cardiac output below initial control and of a further rise in TPR is an additional indicator of uneven matching in cardiac and vascular amplifiers. In our cellophane wrap hypertension experiments, this pattern was observed in the New Zealand white rabbit strain over 4–5 weeks of hypertension (Fig. 3a). But in the English multicoloured rabbit strain cardiac output remained high for up to 12 weeks of hypertension (Fig. 3b), though it tended to fall when the duration of hypertension exceeded 12–15 weeks (unpublished data). In recent longitudinal studies in man there is a tendency for...
cardiac output to decline [16] and in most older hypertensive patients cardiac output tends to be below normal and its capacity to increase during exercise is also impaired (Fig. 2: EH II) [15, 16]. Similarly there is reduction in cardiac performance in older rats with genetic hypertension [43]. All these provide evidence of some limitation of cardiac performance, particularly when compared with continuing enhancement of vascular responsiveness.

An interesting intervention study has been reported in ACTH hypertension, which is normally cardiac output mediated [45]. After pretreatment with β-adrenoceptor-blocking drugs to block the cardiac sympathetic nerves, the initial rise in blood pressure is largely through a rise in TPR, with the rise in output smaller and of slower onset [56]. In these experiments the mechanism underlying the altered haemodynamic pattern was not analysed, but the time course was too rapid to involve structural mechanisms. The experiments suggest that matching of cardiac and vascular contractile performance is always important for chronic maintenance of hypertension through elevation of cardiac output alone.

In summary, the amplifying capacity of the hypertrophied heart does not keep pace with that of vascular smooth muscle, favouring the development of a dominant TPR pattern in longstanding hypertension. This is a pathophysiological change unrelated to normal auto-regulation of blood flow.

Mechanisms of renovascular hypertension

I want to consider two experimental models: 'one-kidney, one-clip' renal artery stenosis (i.e. classic Goldblatt hypertension) and cellophane wrap hypertension, a slowly developing variant of renovascular hypertension. When fully established they have many features in common.

Renal artery stenosis has been studied more extensively than any other type of experimental hypertension. Barger [57] in his Goldblatt Memorial Lecture summarized the current position on its pathogenesis. The early elevation of blood pressure is considered to be almost entirely due to the systemic vasoconstrictor action of ANGII [57–62]. During this 'renin-independent' phase plasma renin and ANGII levels are high and administration of ANGII antagonists and inhibitors of the conversion of ANGI into ANGII restores pressure close to normal [57, 59–61]. Miller et al. [62] observed that when ANGII formation was prevented by pretreatment with teprotide, the production of renal artery stenosis in conscious dogs no longer resulted in hypertension. They therefore considered that ANGII was an important 'trigger' mechanism for the development of hypertension. With continuing hypertension the 'renin-independent' phase develops by about 7–12 days. Plasma renin and ANGII have become restored and ANGII inhibitors have little effect on the blood pressure [61, 63]. The aorta–renal artery pressure gradient during this phase has much the same magnitude as early on and blood volume remains high [63].

In wrap hypertension either both kidneys or the one remaining kidney are loosely wrapped in cellophane [37, 44]. Over the next 4–5 weeks they become gradually encased by a fibrous capsule, which compresses the kidney [44]. The capsule compression forces are about 30 mmHg after about 4 weeks [64]. They create a pressure gradient between aorta and intrarenal vessels, analogous to the changes in renal artery stenosis. Because of the slow nature of the renal compression the plasma renin levels alter minimally, if at all, from the pre-operative control value at any time during development, so that there is no 'renin-dependent' phase as in renal artery stenosis [65].

Hydraulic properties of renal artery stenosis

In their original paper Goldblatt et al. [66] stressed how tight the stenosis had to be to produce chronic elevation of blood pressure, which is in accord with clinical experience. On the other hand, relatively small falls in renal perfusion increase the rate of renin release [58]. Dr Warwick Anderson and I wondered why milder stenosis did not lead to some degree of hypertension. We used conscious dogs with one remaining kidney, with a Doppler flowmeter and constrictive device (cuff or snare) implanted around the renal artery, and with catheters to measure systemic and distal renal artery pressures [67].

We soon learned about the hydraulic complexities of arterial stenosis, which have been subjected to some theoretical analysis [68–71]. The factors determining the resistance to blood flow of any arterial stenosis include the degree of narrowing of the arterial diameter, the upstream arterial pressure and the pressure drop and flow across the stenosis. The last two variables are, in turn, influenced by the tone of the distal vascular bed [67–69, 72]. If the latter is dilated, the degree of narrowing of the arterial diameter required to lower pressure distal to the stenosis to a given level is less than if the distal bed is constricted.

In our experiments we rapidly narrowed the
Sequential analysis of hypertension

FIG. 6. Average haemodynamic effects of 30 min renal artery stenosis in conscious dogs produced by rapidly lowering distal renal artery pressure to 40 mmHg and then maintaining the renal artery cuff clamped for the remainder of the experiment. (a) Normal response; (b) results whilst teprotide (converting enzyme inhibitor) was infused into the renal artery; (c) results during infusion with teprotide; ANGII was infused into the renal artery (stippling) to simulate normal restoration of distal renal artery pressure and reduction in stenosis resistance. Renal blood flow was measured by a Doppler flowmeter and expressed as kHz Doppler shift; n = number of dogs. (Based on [72].)

renal artery by either cuff or snare to lower the distal renal artery pressure to either 60 or 40 mmHg, and then clamped the constrictive device. Surprisingly, there was restoration of the pressure and a return to normal of renin levels after the initial rise (Fig. 6a) [67]. With this degree of stenosis there was only a minimal and transient rise in systemic MAP, suggesting that the restoration of distal renal artery pressure was mainly due to changes in the distal bed. We found that the restoration of the distal renal artery pressure was due to a vasoconstrictor action of ANGII on the renal bed, which was prevented by infusing teprotide into the renal artery (Fig. 6b) or by giving an ANGII antagonist [67]. In the presence of teprotide normal restoration of distal pressure could be simulated experimentally by infusing minute quantities of ANGII into the renal artery (Fig. 6c). The renal constrictor effect of ANGII is mainly on the efferent arteriole, which helps to maintain glomerular filtration rate (GFR) [73].

Almost all vascular beds respond to an acute reduction in perfusion pressure with an autoregulatory vasodilatation [12, 13]. But the kidney is unique in having the pressor hormone ANGII acting on the renal vessels to compensate for the initial vasodilator response (Fig. 6a). Through this local constrictor action of ANGII the resistance to blood flow of a fixed diameter stenosis does not remain the same as at the height of vasodilator response, but becomes smaller with the restoration of distal renal artery pressure (Fig. 6a) [67, 72]. Vascular surgeons have long known that a given degree of arterial diameter narrowing is less 'critical' from the viewpoint of lowering distal pressure or flow if the bed is constricted than if it is dilated [68, 69, 71].
FIG. 7. Average responses over 7 days of renal artery stenosis induced by lowering renal artery pressure to 20 mmHg either (a) by a single rapid inflation of the cuff followed by clamping, in five dogs, or (b) by relowering it four times over 1 h by small additional cuff inflations, with clamping then maintained until day 7, in six dogs. AP, Arterial pressure (mmHg); RBF, renal blood flow (kHz Doppler shift); RVR, renal vascular resistance (as percentage of the average control value); PRA, plasma renin activity (ng h⁻¹ ml⁻¹); C, control day; values at end of 1 h stenosis (1 h) and after 1–7 days of stenosis are shown; R, recovery 24 h after cuff deflation. (Based on [74].)

Renin-dependent phase

The renal effect of ANGII can, in a sense, be regarded as an antihypertensive mechanism, since with the great reduction in aorta–renal artery pressure gradient chronic hypertension does not develop and renin release returns close to normal [74]. With more severe stenosis, produced by lowering the distal renal artery pressure to 20 mmHg, there was an immediate rise in systemic MAP and high renin levels. But again it was not associated with sustained hypertension and after 1–2 days distal renal artery pressure, systemic pressure and plasma renin levels all returned close to initial control (Fig. 7a). Only when the renal artery was narrowed by an estimated 85–90% of its diameter did we get sustained Goldblatt hypertension (Fig. 7b) [74].

The idea that the stenosis resistance made a significant contribution to the rise in TPR has not been seriously entertained since the classic work of Goldblatt et al. in 1934 [66]. They showed that narrowing of arteries other than the kidney (e.g. femoral and splenic arteries) did not produce hypertension. As a result they dismissed the importance of hydraulic resistance of renal artery stenosis. We thought that, because of the
FIG. 8. Changes in systemic and renal haemodynamics during graded progressive stenosis of the renal artery in conscious dogs. C., C,, Control days; the renal artery cuff was inflated to lower distal pressure to 60 ('mild'), 40 ('moderate') and 20 ('severe') mmHg twice daily (23 and 18 h before measurements) on days 1, 2 and 3 of stenosis; R, recovery 24 h after cuff deflation. AP, Arterial pressure; RBF, renal blood flow; CO, cardiac output (kHz Doppler shift); PRA, plasma renin activity. (Based on [75].)

relatively high proportion of the cardiac output flowing through the kidney compared with the vascular beds studied by Goldblatt et al. [66] and the unique hydraulic properties of renal artery stenosis, it was worthwhile to determine the contribution of the stenosis resistance to the rise in TPR. In these experiments the dogs had electromagnetic flowmeters on the aortic root for measuring cardiac output, plus the usual renal instrumentation described above [75].

Measurements were made over 3 days (Fig. 8). On the first day of stenosis distal renal artery pressure was lowered to 60, 40 or 20 mmHg. To obtain a fair range of stenoses, we progressively narrowed the renal artery each day by lowering its distal pressure to the specified value for each dog and making measurements 18 h after each adjustment. At each level of progressive stenosis there were progressive rises over the 3 days in MAP, in plasma renin activity and in the total renal resistance to flow, which was predominantly due to the progressive rise in stenosis resistance. There was a close relationship between renal artery stenosis resistance and the rise in MAP on each day, and between stenosis resistance and plasma renin levels [75].

The rises in stenosis resistance and in TPR obtained after 3 days of 'moderate' (40 mmHg) progressive stenosis were similar to those observed in chronic benign Goldblatt hypertension [74,
and the rise in systemic blood pressure was almost entirely due to a rise in TPR (Fig. 8). The stenosis resistance contributed about 25–35% of the total rise in TPR and MAP; the remainder was mainly due to ANGII-mediated constriction of non-renal peripheral beds (Fig. 9).

In chronic Goldblatt hypertension the stenosis is so tight that the intrarenal action of ANGII cannot alone restore perfusion pressure or maintain renal blood flow as it did in the experiments in Fig. 6(a). It is now the rise in systemic blood pressure which helps to maintain these variables at reasonable levels. As discussed by Anderson et al. [75] the stenosis resistance can make a significant contribution to the overall rise in TPR and blood pressure only if renal blood flow is maintained relatively high and remains a significant fraction of the cardiac output. This probably did not happen in the original experiments of Goldblatt et al. [66] during narrowing of the

splenic or femoral arteries and was the reason why there was so little effect. These vessels normally carry a considerably smaller fraction of the cardiac output than the renal artery, and the distal beds respond to stenosis only by dilatation. No organ other than the kidney produces a hormone like ANGII for local vasoconstriction and for indirectly raising systemic blood pressure and minimizing reduction in blood flow. Thus the high blood pressure produced by the systemic constrictor action of ANGII makes it possible for the renal artery stenosis resistance to remain a significant fraction of the rise of TPR. The contributions to the rise in TPR by ANGII and stenosis resistance are thus closely interrelated.

I now want to consider whether ANGII is the indispensable ‘trigger’ mechanism for development of this type of hypertension as suggested by Miller et al. [62]. They produced renal artery stenosis by lowering distal renal artery pressure to the same level on two occasions. The first experiment determined the normal response, the second was obtained in the presence of teprotide, which abolished the rise in systemic pressure. This suggested that ANGII was essential for developing hypertension. However, teprotide also abolishes the renal constrictor effects of ANGII, so that stenosis now elicits only vasodilatation [67, 72]. Under these circumstances the narrowing of the arterial diameter required to reduce distal artery pressure to a predetermined value will be smaller than when the renal vasculature is constricted by ANGII during the normal response (Fig. 6) [72]. This is most likely what happened in the study by Miller et al. [62], who did not fully appreciate the complex hydraulic properties of the stenosis. We have recently developed a protocol permitting similar degrees of narrowing of the renal artery before and during inhibition of ANGII production. Preliminary findings indicate that the ANGII inhibitor reduces, but does not prevent, the initial rise in blood pressure, which is about 40% of the normal response (Fig. 10) (W. P. Anderson, S. Selig, C. I. Johnston & P. I. Korner, unpublished results). However, depression of GFR is greater than in the presence of ANGII. Thus, in acute stenosis, the action of ANGII is not indispensable for developing some rise in blood pressure, but it has a most important homoeostatic role for maintaining GFR and renal function.

Renin-independent phase

The main factor contributing to the maintenance of elevated TPR and blood pressure
during this phase is the hypertrophy of the heart and vessels, which amplifies systemic stimuli and performs a closely similar function to that performed by ANGII in the early phase of hypertension, i.e. maintaining high systemic pressure and thus optimal renal function (Fig. 11). Together these factors will contribute about 65–75% of the rise in TPR, with the remaining 25–35% still coming from the elevated stenosis resistance.

Even during the ‘renin-dependent’ phase the stenosis resistance in Goldblatt hypertension probably never contributes more than about 25–35% of the rise in TPR. This is because acute
induction of stenosis immediately brings into play the homoeostatic effects of ANGII discussed earlier. But in the much more slowly developing cellophane wrap hypertension (in which there is no significant rise in renin), the initiating cause of the hypertension (the gradually increasing renal capsular compression forces) accounts for a greater proportion of the initial rise in blood pressure. This proportion diminishes with the development of cardiovascular hypertrophy, elevation of blood volume and a number of other changes which together make a progressively greater contribution to the elevated pressure.

This phase of hypertension in renal artery stenosis closely resembles kidney wrap hypertension. Blood volume is elevated in both (e.g. [44, 63]) and autonomic abnormalities are similar (see below), as are some of the changes in cellular membrane properties [78]. The point is that, owing to the amplification provided by the hypertrophy of the heart and vessels, only a very small increase in the normal level of physiological stimuli is needed to account for 65–75% of the hypertension. This can be provided by some of the above mechanisms, e.g. a slight rise in sympathetic activity [79, 80] or depression of Na\(^+-\)K\(^+\) pump, which enhances cardiovascular contractility [78].

At least some of the changes in autonomic function are secondary to the circulatory alterations in hypertension, and their homoeostatic role in the elevation of pressure is readily apparent. For example, the main cause of the depression of vagal gain and effector response range of the baroreceptor–heart rate reflex in rabbits with cellophane wrap hypertension appears to be secondary to the changes in total (and probably in central) blood volume (Fig. 12). Treatment with diuretics and by \(\beta\)-adrenoceptor blockade, which produced a relatively small reduction in resting MAP, restored the vagal component of the reflex (Fig. 12) (P. I. Korner & D. W. Blake, unpublished results). Parenthetically, there is nothing distinctive about the effects of renovascular hypertension on the properties of the baroreceptor–heart rate reflex, and similar changes occur in essential hypertension [81–83].

Clearly, if in the presence of the cardiovascular amplifiers the activity of the renin–angiotensin system continued at the levels observed during the renin-dependent phase this would rapidly lead to malignant hypertension, with catastrophic consequences for the organism. In the renin-independent phase renal perfusion pressure and blood flow are often below normal, which will tend to maintain some elevation in renin secretion [58]. Thus it seems likely that reflex mechanisms contribute to the almost complete restoration of renin levels. We have recently observed reduction in plasma renin levels in normal rabbits during systemic vasoconstriction and bradycardia produced by intravenous infusions of methoxamine and during mild systemic vasoconstriction associated with intracisternal infusions of minute quantities of ANGII (P. I. Korner, J. R. Oliver, J. A. Angus & M. J. Lew, unpublished results). Both manoeuvres elevate central blood volume, suggesting that the reflex reduction is mediated through central nervous system interactions involving cardio-pulmonary and arterial baroreceptors [10, 84].

Renal blood flow is reduced in both stenosis [63, 74] and wrap hypertension (W. P. Anderson & K. Denton, unpublished results) and the depression of GFR probably contributes to the elevation of blood volume. All factors, apart from the stenosis resistance, can be regarded as homoeostatic adjustments to maintain optimum renal function in the face of a tight stenosis, in the same way that ANGII was the major homoeostatic mechanism in the acute ‘renin-dependent’ phase (Fig. 11). It is the stenosis resistance (or capsular compression forces) that are the basic cause of the hypertension and only their removal produces permanent cure (Fig. 7).

In summary, the reason why renal artery stenosis has to be tight to produce permanent hypertension relates to its complex hydraulic
properties. Its resistance contributes about 25–35% to the rise in MAP. The rest comes from the elevation of ANGII, raised blood volume and cardiovascular hypertrophy and some cellular changes. These can all be regarded as homeostatic adjustments to maintain renal function.

**Essential hypertension**

In human essential hypertension patients first present themselves when the disorder is fully established and little is known about the early development. To obtain some insight about this important phase of the disorder there has been much effort to study young hypertensive subjects, including those with labile or borderline hypertension, but this has provided less information than had been hoped.

There has been an enormous effort in the search for abnormalities and many functional disorders have been described (e.g. [85]). These include alterations in sympathetic activity [86],

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**Fig. 12.** Vagal component of baroreceptor heart rate reflex in (a) 12 sham-operated and (b) 12 renal cellophane-wrapped rabbits. Sigmoid mean arterial pressure–heart period curves obtained during β-adrenoceptor blockade to block cardiac sympathetic activity. C, Pre-operative control (○); period I, 6 weeks after operation (▲); period II (Rx), after 2 weeks treatment with timolol (4 mg/kg twice daily, intramuscularly) + frusemide (2 mg day⁻¹ kg⁻¹, intramuscularly) given to six rabbits in each group from 6 to 8 weeks and in six rabbits from 8 to 10 weeks (◇); period II (No Rx), 2 weeks without treatment, i.e. before treatment in six rabbits and after treatment in the rest (●). In renal wrapped rabbits treatment produced only a small reduction in resting blood pressure but restored gain and heart period range (D.W. Blake & P.I. Korner, unpublished data).
The problem is to decide whether all these factors are basic causes contributing to the development of essential hypertension from the start. An alternative view is that the pathogenesis is similar to that of 'secondary' types of hypertension, with basic initiating cause(s), not necessarily the same in all individuals, and with other factors playing a more homoeostatic role (e.g. as in Fig. 11 for renal artery stenosis).

In renovascular hypertension we have seen that once the hypertension has become fully established, the cardiovascular hypertrophy, rise in blood volume and other homoeostatic factors contribute more to the elevated blood pressure than the basic initiating mechanism. This will also apply to the relative contribution of the basic and homoeostatic mechanisms elevating blood pressure in other types of 'secondary' hypertension. There is every reason to believe that this will also apply to established essential hypertension.

The hypothesis of distinctive cause(s) initiating essential hypertension differs from the mosaic theory of Page [92], which suggests multiple causes without considering the sequence in which they appear. This theory has had an important influence on the thinking about pathogenesis since it was formulated in 1949, and restated in 1965 and 1979 [92–94]. Page & McCubbin [93] stated: "Its view was to recognise the multifaceted nature of the problem. In this way it differs radically from other theories that suggest a singular disturbance".

There is no doubt that when any type of hypertension has become fully established many factors contribute to its maintenance. Moreover, it is no longer possible to determine with assurance the initiating cause unless, as in 'secondary' types of hypertension, there is either an anatomical defect or a persistent functional abnormality. However, in patients with uncomplicated hypertension the role of the structural cardiovascular amplifiers and related homoeostatic factors is as great in the experimental types of hypertension discussed earlier, and their contribution to the maintenance of the hypertension must be similar [4, 5, 49, 95]. Therefore the basic causes of the hypertension need account for only about 25–35% of the rise in pressure, much as in renal artery stenosis. To qualify as a basic, initiating cause the abnormality must be present both at the beginning of hypertension and during the established phase. Hence, sequential analysis of the development of essential hypertension in individual patients may have something to offer.

Redevelopment of hypertension

We recently studied the haemodynamics of a group of patients with established essential hypertension before treatment and after 1 year's satisfactory control of their blood pressure by conventional drug therapy [96]. On each occasion measurements were obtained before and after autonomic blockade. The level of TPR after blockade provides an index of the hypertrophy of the resistance vessels [49]. The second study was performed 1 month after withdrawal of diuretics and several days after withdrawing the other drugs, so that we could be sure that the effects observed were due to the reversal of the hypertension and not due to the residual effects of the drugs.

At the time of the second study the non-autonomic component of TPR, which initially had been markedly elevated, was completely normal (Fig. 13), i.e. it had returned to the range of the non-autonomic component of TPR in normal subjects [95, 96]. An important effect of drug therapy of hypertension is therefore that it reverses the vascular hypertrophy and lowers the gain of the vascular amplifiers so that they are less responsive to pressor stimuli than before treatment. Cardiac output was higher on average than during the first study (Fig. 13) [96]. An adequate analysis of cardiac function was not undertaken, but the ECG showed less marked left ventricular enlargement.

In each patient blood pressure rose when anti-hypertensive treatment was withheld and in those followed up before treatment recommenced it had returned to the original hypertensive levels within 4–20 weeks (Fig. 14). The study suggests that, although standard antihypertensive drug therapy reverses the hypertrophy and some of the related secondary changes of hypertension, the primary cause(s) of the elevation in blood pressure are still present in each individual.

We have here an opportunity of studying the redevelopment of essential hypertension after reducing or reversing the cardiovascular hypertrophy. We cannot be certain that the factors leading to the redevelopment of hypertension are the same as those that produced the original elevation of pressure, but it seems a reasonable
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21s

Resting Autonomic

I

II

I

II

FIG. 13. Results in 13 patients with essential hypertension showing average mean arterial pressure (MAP), cardiac index (CI) and total peripheral resistance index (TPRI). Study I, before start of treatment; study II, after 1 year's antihypertensive therapy and a few days after withdrawal of drugs. Normal resting values (left) and values obtained after autonomic blockade (right) are shown. The bar is 1 SED within patients; *P < 0.05. (Based on 1951.)

hypothesis. Since the study by Jennings et al. [96] we have developed methods for measuring cardiac output non-invasively and sequentially. It should now be possible to determine whether redevelopment of hypertension occurs through a rise in cardiac output or through a rise in TPR, and whether the pattern changes over the first few weeks.

At present we still have no definite evidence whether essential hypertension is a disorder with uniform primary cause(s) or whether there are subsets of patients with diverse primary causes. The latter appears likely, from findings in animals with genetically controlled hypertension. Various gene combinations controlling different body functions can lead to development of hypertension through different basic mechanisms in the different animal models [97–102].

Sympathetic overactivity and increased sensitivity to salt have been regarded as strong candidates for primary causes in human hypertension. At one time it was thought that all patients had increased activity of the sympathetic nervous system [103–106] because the amplifying effects of the hypertrophied vessels were not recognized [4, 49, 51, 95]. These account for the apparent elevation of the neural component of resting TPR in hypertensive subjects, and also for the greater reflex rises in blood pressure and TPR during constrictor reflexes than in normal subjects [107, 108].

More recently biochemical indices of sympathetic function have been developed, e.g. measurements of plasma noradrenaline and/or adrenaline [86]. In some series elevations in catecholamine levels have been reported [109–112]. But Kopin et al. [113] have concluded recently that, when the effect of age on plasma catecholamine was taken into account, the average differences in catecholamine levels were not significant.

However, there may be a subset of patients with sympathetic overactivity. Esler et al. [114] have measured noradrenaline 'spillover' rate into plasma, its clearance and the disappearance of \(^{3}H\)noradrenaline. Spillover rate is only a minute fraction of the rate of transmitter release at sympathetic synapses, but is assumed to be proportional to the latter [86]. The greatest differences between hypertensive and normotensive subjects were in the \(^{3}H\)noradrenaline disappearance curves. This curve has two exponentials and the first of these provides a measure of reuptake of transmitter after release at the nerve ending. In eight of 37, or about 20% of patients, its half-time was significantly higher than in any normal subject (Fig. 15). In these subjects noradrenaline 'spillover' rates were about twice as high as in normotensive subjects [114].

Thus, in about 20% of patients with defective reuptake at the peripheral sympathetic terminal, released transmitter would exert longer lasting effects. In this group sympathetic overactivity occurs entirely through a fault in a neural membrane pump. This type of defect cannot be readily eliminated through the normal mechanisms of the body's cardiovascular control system. We cannot yet be certain that such a fault actually causes elevation in pressure, but it is of the type that could produce permanent hyper-
tension. Similarly there appears to be a considerable range of sensitivities to salt in a given population [87, 102, 115, 116]. Several defects of sodium transport systems have been described, some of which appear to be genetic (e.g. [90]) and some a consequence of hypertension and present also in experimental types [78, 117].

In the analysis of redevelopment of hypertension it will be possible, through sequential haemodynamic and blood volume measurements, to classify patients with essential hypertension more precisely into those with initial elevation of cardiac output or TPR. Similarly, it will be possible to characterize patients from the point of view of whether autonomic function is abnormal at the start, if and how it becomes altered with time, whether there are abnormalities in cellular mechanisms present throughout redevelopment etc. The sequential study of the development of essential hypertension should allow us to sort out 'primary' from homoeostatic factors, much as in experimental hypertension. It should also answer the question whether patients with essential hypertension are a homogeneous or a heterogeneous group.

In summary, the study of essential hypertension is particularly difficult during the establishment phase, when homoeostatic factors over-
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FIG. 15. Lower graph: half-times of first (rapid) exponential components of $^{3H}$noradrenaline disappearance curve from plasma in normal subjects, patients with essential hypertension and patients with peripheral and central autonomic neuropathies. Upper graph: half-time of the first exponential represents neuronal re-uptake of transmitter at the sympathetic terminal, since it was prolonged by desipramine (which blocks neuronal uptake) but not by cortisol (which inhibits extraneuronal uptake) (from [114]).

Conclusions

‘Primary’ (essential) hypertension and the various types of ‘secondary’ hypertension in their fully developed forms are associated with multiple disturbances of cardiovascular control. The mosaic theory of Page implies a multiplicity of originating causes for every type of hypertension, and certainly many factors maintain the high blood pressure in established hypertension. However, the mosaic theory describes essential hypertension at only one point in time, when it is fully established. I wish to propose that essential hypertension is similar to ‘secondary’ hypertension such as renal artery stenosis, where there is a clearcut initiating abnormality and where some of the other mechanisms maintaining high blood pressure have a clearcut ‘homeostatic’ role, e.g. to maintain renal function. Moreover, in established hypertension the initial cause will generally make a smaller contribution to the elevation in pressure than the homeostatic factors.

The action of the cardiovascular amplifiers appears to be the chief homeostatic factor contributing to the maintenance of high blood pressure in every type of established hypertension. In severe prolonged hypertension, cardiac hypertrophy does not keep pace with vascular hypertrophy, so that cardiac output can no longer be maintained at as high an arterial pressure. This eventually leads to maintenance of hypertension through high TPR, even when the change was initiated by elevation of cardiac output. The changes in haemodynamic patterns are a pathophysiological consequence of the different effects of chronic pressure load on hypertrophy of the heart and vessels, and have nothing to do with normal autoregulation.

A new approach to finding the basic causes is to reverse the structural changes with prolonged anti-hypertensive treatment and then study redevelopment of hypertension. This may improve our ability to classify patients with essential hypertension, and find out whether this is a disorder with uniform cause(s) or whether there are subsets of patients with different basic cause(s). In the latter case it may allow more specific therapy in patients with essential hypertension, directed at the basic cause of the disorder in each individual.

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