Concepts in Hypertension
The Croonian Lecture 1979

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In considering concepts of hypertension I must emphasise that very few are new, many having a venerable ancestry that has often been re-expressed in different language.

Definitions of Hypertension

It is impossible to discuss hypertension without defining it. There are many ways of doing this and some of them are shown in Table 1. I have put the first in that form

Table 1. Definitions of Hypertension.

1	Never define, describe quantity (Pickering).
2	Statistical deviation from young adult B.P. (say 120/80).
3	Deviation from mean of whole population at given age (standard deviation units).
4	Working or insurance definition: level which is associated with increased morbidity and mortality at some future time (5-20 yrs) compared with whole population (excess mortality).

since, as Pickering has emphasised, blood pressure for populations is a continuous variable and any cut-off point has to be arbitrary[1]. In a sense, therefore, it is better not to discuss hypertension as such but to give the figures for the blood pressure linked with prognosis. The second point relates to the question of whether the rise of blood pressure with age, characteristic of western civilisation, should be regarded as pathological. If so, and this is my belief, the blood pressure of a young adult should be regarded as the desirable level and hypertension can be regarded as a deviation above. The third point brings in the concept of a blood pressure 'normal for age', for the word normal can be misused and must be clearly defined. It can indicate the mean for a population at a given age and the individual deviation from that mean is then expressed in standard deviation units. The last, which I have called a working definition, is the one behind most clinical decisions and relates to the increased morbidity and mortality at some future time, which the doctor is trying to avert by adequate treatment.

Rise of Blood Pressure with Age

Concealed within the rising curves shown in Fig. 1[2] is the knowledge that the blood pressure does not rise with age in everyone, nor even in the populations of isolated communities in Pacific islands or in Africa, which emphasises the probable pathological nature of the rise of mean blood pressure for most civilised populations[3, 4].

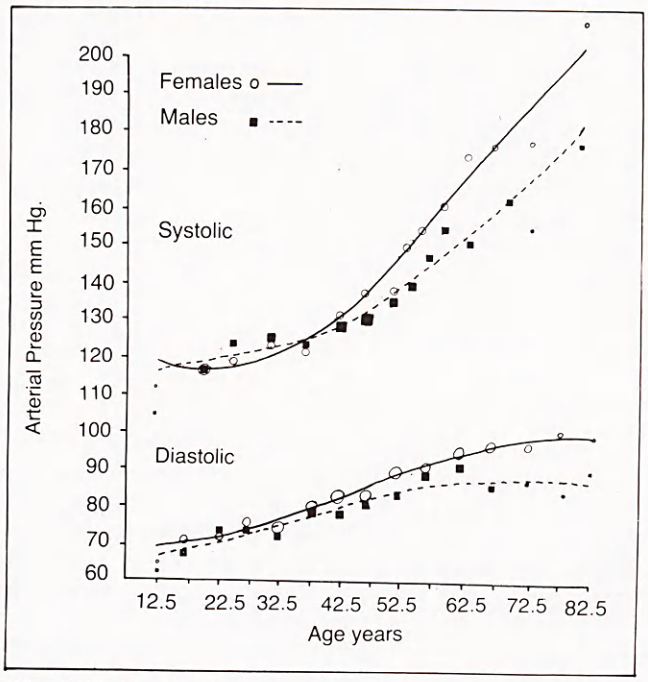

Fig. 1[2]. *Systolic and diastolic pressures for females and males for each 5-year age group of the population sample, together with the fitted curves. The area of each circle or square is proportional to the number of subjects in that age group.*

Nature of the Rise

Extensive studies, such as those by Voors and his colleagues[5], have shown that in cross-sectional measurements on large populations of children, most of the rise that occurs as the young child grows towards puberty can be explained on the basis of changes in height and weight rather than in age itself. Given the height and weight of a child, accurate prediction of its blood pressure is possible. Height is a well-known inherited characteristic[6], so the heritability of the related blood pressure is introduced. From other studies it is known that the blood pressure of members of a family is quite closely related[7] and a most important concept which has been advanced is that of 'tracking'. This indicates that the course followed by the blood pressure of an individual is determined from an early age and any rise that occurs is progressively steeper and is proportional to the starting pressure, so that the lower the starting pressure, the smaller the rate of rise. It

is probable that this does not become apparent in most of our populations until early adult life, since many large surveys have been unable to distinguish big differences between populations until that time. For example, young blacks and whites up to the age of 20 could not be distinguished by means of their blood pressure distributions[8], though later in life the mean blood pressure for the blacks exceeds that of the whites[9].

Two major pieces of evidence strongly support the concept of tracking. Miall and Lovell [10] re-measured the blood pressure of a cohort of subjects in South Wales at long intervals after the initial measurement. They showed that the rise of pressure was closely related to the starting pressure and that age was not the factor concerned. This was confirmed in a much larger study from the USA by Harlan and his colleagues[11]. In 1940 they measured many physical characteristics in a cohort of healthy young naval pilots and followed them at intervals during the next 30 years. The rise of blood pressure with time was related not to age but to the starting pressure, and the higher this became at each successive measurement, the more rapid was the subsequent rise. The popular phrase 'the rise of blood pressure with age' should therefore be discarded.

Family Aggregation of Blood Pressure

The blood pressure in families tends towards the mean so that parents and children resemble one another in terms of blood pressure, as do siblings[12, 13]. However, this fact cannot be used to indicate a genetic factor, because environmental influences may start *in utero*. In a study of Canadian families who had adopted children as well as their own natural ones, Mongeau and his colleagues[14] found that the adopted children did not resemble either the parents or the natural children in terms of blood pressure, implying that inheritance is more important than environment in the early determination of blood pressure level.

Labile Hypertension

As emphasised in Table 2, this is a most dangerous concept, since it has been shown for a very long time that most blood pressure, whether measured by intra-arterial recording[15] or by a portable machine[16], is highly labile[17]. An extremely high blood pressure in the daytime may drop very considerably during sleep; some subjects may have marked hypertension in response to certain situations during the day, yet at other times have quite low blood pressures. We know from other studies that only about 20 per cent of those regarded as having a labile blood pressure when young will have a much higher pressure requiring treatment when studied 20 years later[18]. Therefore, if initially they are all given the label of labile hypertension and their characteristics from a haemodynamic point of view appear the same, it seems to me that the selection itself has created group characteristics for a false entity. These characteristics have been called in physiological terms a defence reaction, and studies by Brod and his colleagues[19] show that stimuli such as mental arithmetic produce changes that could be regarded as those of an anxiety state. Cannon[20] coined the phrase 'Fight or flight' for these emotional reactions. There are many studies on groups of individuals with these characteristics[18, 21] and I think that the term 'labile hypertension' should be dropped and the term 'labile blood pressure' put in its place.

Table 2. Labile Hypertension.

1	Misnomer: should be labile blood pressure Cohort longitudinal studies.
2	Investigated: selection creates group characteristics.
3	Defence reaction: Increased heart rate, cardiac output, muscle flow Decreased skin and kidney flow Anxiety state?

Baroreceptors

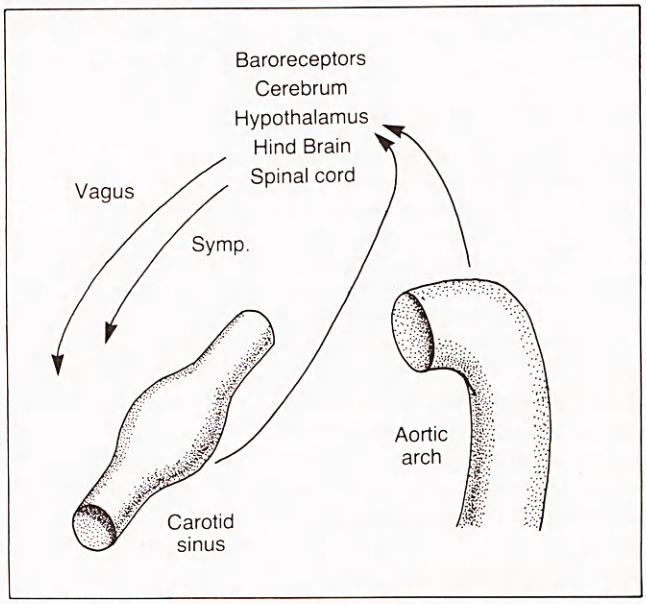

Fig. 2. *Diagrammatic representation of some important afferent and efferent pathways in acute control of blood pressure.*

It is obvious that if the baroreceptors diagrammatically shown in Fig. 2 were designed to play a long-term role in the control of blood pressure, a high blood pressure could not exist without considerable modification in baroreceptor performance. The concept that essential hypertension is due to changes in the carotid and aortic baroreceptors is a very old one and was first seriously propounded by Heymans and his colleagues[22, 23]. He believed that pathological change, particularly in the wall of the carotid sinus, led to lack of distensibility and therefore lack of sensitivity of the stretch receptors and a consequent high blood pressure. This view has been supported by Angell-James[24, 25] who showed in rabbits with hypertension due to a variety of causes, including renal, that they all had the common feature of pathological change, especially in the aortic wall, together with a lack of distensibility of the aorta and a low rate of firing of the aortic baroreceptors. More recent work in man has

shown definite changes of the carotid baroreceptor response in hypertension[26-28]. This does not answer the question of whether the hypertension itself causes the change in most circumstances, and therefore the baroreceptors merely allow its perpetuation. The situation was made much clearer by the old experiments of McCubbin and his colleagues[29] who showed in the dog with renal hypertension that the carotid baroreceptors rapidly re-set at the higher pressures. The rate of firing decreased, so it required a much higher pressure to cause firing at the same rate as in a dog with normal blood pressure. This clearly indicates to me that the baroreceptors as they exist are only interested in acute changes of blood pressure. From an evolutionary point of view, it might be asked why there should be baroreceptors interested in the long-term control of high blood pressure. Presumably the height of the blood pressure would have little evolutionary importance so long as it did not interfere with reproduction, and, from an immediate point of view, if high pressure does not interfere with tissue flow, the baroreceptors would not assume much importance in the long term. I suggest that tissue flow is the most important point of stability in the circulation, however it may be achieved. This allows the reintroduction of the Bayliss concept[30] in which the arterioles governing tissue flow constrict at higher pressures and relax at lower ones, giving a 'myogenic' tissue autoregulation. There are still other areas that deserve deeper study and I have always thought that the older studies on patients who have had their spinal cord transected about C3 raise questions that may be of great importance in normal subjects. The acute rise of pressure induced by either a full bladder or percussion over the bladder region is most remarkable, from figures like 90/60 to 250/120 mmHg, and Guttmann and Whitteridge[31] showed the haemodynamic consequences. This phenomenon is usually explained as a spinal reflex that cannot be inhibited, presumably through a vagal reflex in part, but there must be other pathways not yet defined since the vagus is intact in these subjects. Furthermore, the plasma noradrenaline rises to quite high levels with such a stimulus[32], in distinct contrast to the lack of response both in terms of blood pressure and of noradrenaline when these subjects are tilted[33].

Sympathetic Nervous System

The list of areas of influence of the sympathetic nervous system shown in Table 3 recalls the discussion on labile hypertension and the defence reaction, and indeed the concept of over-activity of the sympathetic nervous system being a cause of high blood pressure is very old. The question that must be posed, however, is whether it is possible to measure accurately sympathetic nervous activity in man. At its extremes there is little doubt that the plasma noradrenaline level does reflect under- and over-activity of sympathetic discharge. Patients with high spinal cord transection have very low levels of plasma noradrenaline even when their blood pressure falls on head-up tilting. The same is true of many patients with the sympathetic degeneration of the Shy-Drager syndrome[34, 35]. What is less certain is whether elevation of plasma noradrenaline may be as readily correlated with sympathetic over-activity. It does seem likely, and some years ago Louis and his colleagues[36] claimed a close correlation between rise of blood pressure and rise of plasma noradrenaline, and others have stated that this is a common occurrence in hypertension. My colleague Sever, in studying various populations, both white and black and with widely distributed blood pressure levels, has shown that a rise of plasma noradrenaline correlates best with age and not with blood pressure[37]. There seems to me very little convincing evidence that sympathetic nerve over-activity is a cause of maintained high blood pressure, as opposed to a labile blood pressure [38, 39], and there is still a need for accurate measurements of pressor sympathetic action.

Table 3. The sympathetic nervous system: possible relationships in hypertension.

Heart rate and cardiac output
Arteriolar resistance
Venous tone
Kidney — renin release
Circulating noradrenaline and adrenaline
Baroreceptor modification

Relative Importance of Different Parts of the Circulation

In the simplest concept of the circulation it is necessary to consider cardiac output and the force of cardiac contraction, the peripheral resistance largely within the arterioles, the venous capacitance vessels in which resides most of the blood volume, and the integration of these variables. It will be noticed that the capillaries are omitted. This is not because they lack importance but because, in relation to high blood pressure, relatively little work has been done on capillary fluid exchange. This is surprising since there has been so much talk about 'volumes' within and without the circulation and, of all the regions playing a large part in control of intravascular volume, the capillaries are of prime importance. Most work has been done in the study of capillary filtration pressure in animals[40] and I am sure that this is an area of research requiring fuller application in man even though some interesting studies have been published[41-43].

Preservation of Equilibrium in the Circulation

There is one major concept, which was first expressed by Claude Bernard as the 'constancy of the *milieu intérieur*[44]. After a long gap this reappeared in 1929 as the principle of homeostasis elaborated by Walter B. Cannon[45]. He re-emphasised both the resistance to change and restoration of the previous state. In hypertension, Borst utilised this concept in looking at the effects of liquorice, a DOCA-like substance, in man[46]. The effects were to raise the blood pressure quickly, and at the same time there was a rise of venous pressure, extracellular fluid volume, and body weight, together

with a positive sodium balance. He drew attention to the fact that while the treatment was continued, there was a return to or towards the starting state of all these variables except the blood pressure, which was maintained even after complete cessation of treatment. He then went beyond the concept and introduced one of his own in which he gave primacy to the kidney, saying that in essential hypertension the kidney required a higher blood pressure to excrete the same sodium load as a normal kidney could excrete at a lower pressure. The consequences were that sodium and water were initially retained by such a kidney, leading to increased plasma volume, increased cardiac output and increased arterial pressure. This sequence was supported and extended by Ledingham[47] and Floyer[48] and their colleagues and considerably amplified by Guyton and his colleagues[49].

The place of increased cardiac output as a primary or even secondary factor in hypertension has not often been supported by hard and lasting evidence[50]. The major missing link in this hypothesis was that, with the rise of cardiac output, the peripheral resistance had to increase, or at least not to decrease, so that the blood pressure could rise. Guyton has provided both theoretical and experimental backing for the truth of this concept and at the same time has added a new all-embracing phrase 'whole body autoregulation', a concept that allows shifts of volumes, cardiac output, pressures, resistances, and excretion of water and salt to preserve both the *milieu intérieur*, homeostasis and all else. However, many have shown that this tidy sequence need not apply in many forms of experimental hypertension which may develop in the presence of severe water and sodium deprivation, without any change in cardiac output or plasma volume[51-55]. The only consistent change has been a rise in peripheral resistance.

Role of the Kidney

It would be well to examine certain aspects of renal behaviour in relation to the supposed primacy of the kidney. In most studies the renal plasma flow in essential hypertension is reduced[56] and, on the whole, the higher the blood pressure, the lower the renal plasma flow. An old observation is that in hypertension an intravenous sodium load is excreted faster than in normal subjects[57, 58], and that surgical or medical treatment of the hypertension returns this variable to normal[59, 60]. It is therefore of great interest that large-scale family studies on the children of parents with a raised blood pressure have paradoxically shown an increased renal plasma flow[61]. Of equal interest are the observations by Slater and his colleagues[62] on young adults, of whom one parent had high blood pressure. About half showed an increased rate of sodium excretion even though the mean blood pressure was not different from a control group. Since this is the behaviour of subjects with established hypertension, the conclusion must be either that the circadian level of pressure was higher in some of these individuals or that the renal fault preceded change of blood pressure. These are paradoxes that need further study, as does the aggregation of urinary kallikrein excretion observed in families by Kass and his colleagues[63]. The reason for its introduction here is that urinary kallikrein is believed to be derived purely from the kidney, and to vary with water and salt excretion and aldosterone secretion[64-67].

Renal Artery Stenosis

Perhaps the clearest example of a primary renal cause of hypertension in man and experimental animals is renal artery stenosis, and, as shown in Table 4, the prediction of a surgical cure may be related to renal ischaemia that

Table 4. Renal Artery Stenosis.

Prediction of surgical cure.		
1	Youth and short duration of hypertension	
2	Good renal function	
3	Stenosed side: Increased water reabsorption	Ratio 1.5/1
	Increased renal vein renin concentration	Ratio 1.5/1
4	Hypotensive response to angiotensin blockers	

can be demonstrated by functional changes in excretion of water and sodium or alterations of renal vein renin concentration[68]. I feel that the most consistent indicator is the renal excretory function but the subject allows discussion of the role of renin in hypertension.

Renin and Angiotensin

In experimental renal clip hypertension the ability of a synthetic competitive peptide angiotensin antagonist (saralasin) to lower the pressure is directly related to the plasma renin activity. I believe that this applies to practically all forms of hypertension in which renin has been implicated and that it is the levels of renin and angiotensin II in the circulation that are important[69]. This reduces the importance of the concept of vascular hypersensitivity and of the view expressed by Swales[70] that renin in the blood vessel wall is important.

Secondary Hypertension

I have observed, like many others, that removal of the supposed primary cause of hypertension is not always followed by a fall in blood pressure. I have seen this in association with phaeochromocytoma, Conn's syndrome, Cushing's syndrome with bilateral adrenalectomy, and renal artery stenosis with nephrectomy. I like to call this the Wilson and Byrom principle[71], since they were the first to point out that, in the rat with renal clip hypertension, removing the kidney beyond the clip only led to a fall in blood pressure if the opposite kidney was free of secondary vascular changes. Since ultimately the intrarenal blood vessels are always affected, the more so the higher the blood pressure, it becomes proper to ask whether all forms of high blood pressure end up as renal[72]. Goldblatt, who championed the primary role of the kidney in all forms of hypertension, was led from his observations on the intrarenal arterial narrowing seen under the microscope in the kidneys of hypertensive

patients, to produce experimental hypertension by the application of a clip to the main renal artery[73]. In renal failure most patients who have become sodium and water overloaded develop high blood pressure, and reduction of body sodium and water usually reduces the pressure[74].

Change in Peripheral Resistance

Folkow[75], in a beautifully argued and presented set of experiments in man and animals, has shown that thickening of the arteriolar wall with a reduced lumen is a universal feature. He showed that the consequences are increased pressure or vasoconstrictor responses to a variety of stimuli and, most important, that in experimental hypertension this wall change may occur very quickly (Fig. 3). The continued maintenance of high

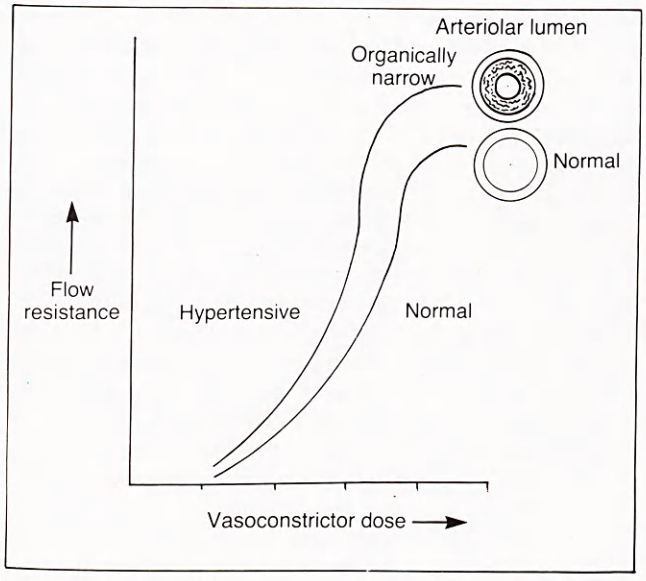

Fig. 3. *The Folkow concept. This shows diagrammatically that vessels from subjects with hypertension have increased resistance at lower doses of vasoconstrictors on the basis of a smaller arteriolar lumen (increased wall to lumen ratio)[75].*

blood pressure after removal of the primary cause should perhaps be sought in this wider change rather than narrowly within the kidney. In relation to essential hypertension, it could be argued that if the change described by Folkow was primary, all else would follow. Equally, since it occurs presumably in most categories of high blood pressure, it must always play its part. If the baroreceptor areas are also incorporated, the hypothesis becomes even more inclusive.

Increased Sensitivity or Reactivity of the Arterial Wall

With vasoconstrictors, a narrow blood vessel must necessarily produce a different resistance to flow with vasoconstrictor agents compared with the wider lumen of the normal vessel. Bohr[76] therefore measured the tension developed in response to different stimuli in a spirally cut

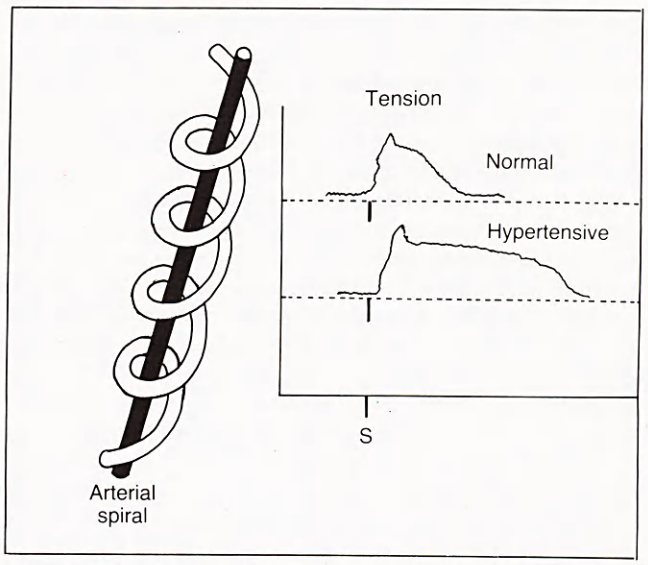

Fig. 4. *The Bohr technique. The arterial spiral cut on a glass rod is attached to a pressure transducer, while being superfused, to produce the tracings shown on the right, reflecting changes of tension in response to different stimuli. The 'hypertensive arteriole' shows a brisker and more prolonged response[77].*

artery attached to a transducer. He showed, for example, that in an animal with hypertension induced by DOCA, the arteries were more reactive and had a prolonged response compared with the normal (Fig. 4). Changes in ionic flux such as those of calcium have received some attention but are not conclusive[78] and the older concept of increased sodium and water in the vessel wall[79] remains unsubstantiated, owing to the old difficulty of distinguishing the muscle cell from other tissues[80].

Important Interrelationships

Some important interrelationships are shown in Table 5. Hypotheses in which very full consideration has been given to the changes and interrelationships of the variables shown have been advanced by Guyton *et al.*[49] and Brown *et al.*[81]. However, a concept I would like to see attacked at every possible opportunity has been introduced elsewhere. The use of the term 'inappropriate' has been so loosely and thoughtlessly applied that it has become debased. As first used in relation to the excessive production of ADH by a tumour of the lung, it had some meaning, and, on the whole, the production of substances by tumours could always be regarded as inappropriate. The term is now used in the sense that levels,

Table 5. The various factors involved in blood pressure control whose interrelationships appear in most hypotheses and to which relationship the term 'inappropriate' is frequently applied.

Renin	ECF volume Plasma volume	Peripheral resistance	BP
Aldosterone	Packed cell volume Na Ex	Cardiac output	

concentrations and volumes behave in a way the observer thinks they should not. This implies that the observer knows why they move as they do. I would suggest that this use of the term obstructs clear thought. If, for example, the importance of tissue blood flow is substituted for the importance of blood pressure, some of the inappropriateness might disappear, and I would suggest that explanations for the unexpected change are sought. I will not discuss all the often contradictory pieces of evidence involving the variables noted in Table 5, but will single out some excellently conducted investigations supporting my point of view. Terminal renal failure with its change of body fluid volumes has offered the greatest of the inappropriate exercises. Onesti and his colleagues[82] showed that when the anaemia of renal failure was corrected, while plasma volume, body weight, and sodium content were maintained by careful ultrafiltration, the previously raised cardiac output dropped and the peripheral resistance rose. Further, McGrath and Ledingham[83], using an angiotensin II antagonist (saralasin), showed that while the drop in blood pressure induced was directly related to plasma renin activity, there was a separate excellent correlation of blood pressure change with plasma volume. These studies seem appropriate and to the point.

The Unmasking Concept

This concept is an extension of the above viewpoint, but seems even worse in its looseness of thought. The concept concludes that when an angiotensin blocker is given to a subject or patient and fails to produce a fall in blood pressure, the renin and angiotensin system was playing little if any part, and that its real role may be unmasked or uncovered by the use of a low sodium diet followed by a diuretic, usually frusemide, and the use of tilting. The resultant fall in blood pressure is considered to have dragged out into the open the reluctant cause of the trouble[84, 85]. The truth, I would suggest, is otherwise and is illustrated in Fig. 5, where, if the prevailing blood pressure is divided into percentages supported by different systems, the effect of sodium and volume depletion is to change those proportions and thereby to render the subject more susceptible to the angiotensin blockade. It is not an unmasking; it is a change, and there should be no surprise if a normal subject on a low sodium intake then responds to saralasin by a drop of blood pressure[86, 87]. Angiotensin may then be regarded as supporting a much higher percentage of the prevailing blood pressure than under usual circumstances.

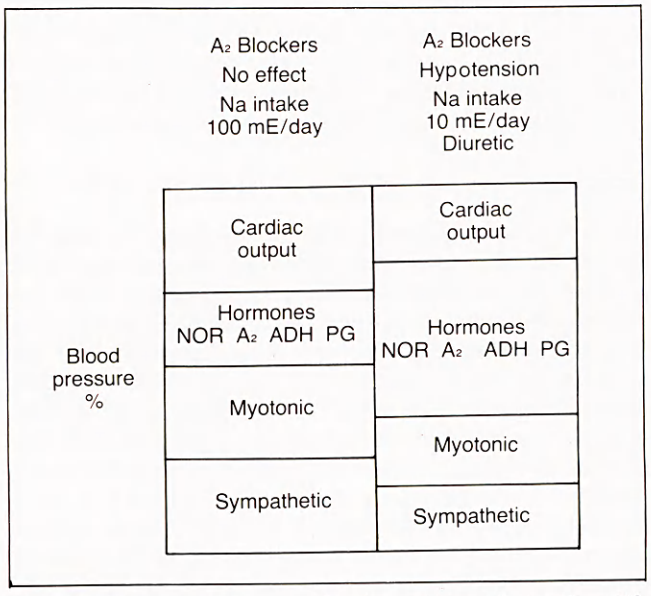

Fig. 5. *A suggested quantitative approach to the different effects of angiotensin blockers on blood pressure. In the left panel the proportional effect of different factors is given a theoretical value in a subject receiving 100 mEq of sodium per day, where the level of angiotensin is so small that the blocker has no effect. In the right-hand panel, in a subject given a low sodium diet and diuretic acutely, the proportion of the blood pressure due to circulating angiotensin II is much greater and the blocker then reduces the blood pressure.*

Low Renin Groups

Shown the data in Table 6 there would be no difficulty in suggesting the diagnosis of Conn's syndrome with the presence of a tumour in one adrenal gland, and since this is the prime example of a condition with a low plasma renin activity, I wish to consider its associations. The treatment of such a patient with spironolactone[88] reveals that the fall in blood pressure was associated with a fall in the high exchangeable sodium and a rise in the low exchangeable potassium. The low renin activity rose into the normal range as the blood pressure fell. Conversely, when treatment was stopped, the exchangeable sodium and extracellular fluid volume rose and the renin activity fell. Schalekamp and his colleagues[89] have recently amplified this sort of observation on a large number of patients but these are associations which do not enable us to say what is the ultimate cause of the high blood pressure. It is worth remembering that Bohr found vascular hyperreactivity in animals with experimental hypertension induced by DOCA[77], so undue emphasis on volumes, even in this condition, may be misleading. The systematic measurement of plasma renin by Brown and his colleagues[90] revealed that in 20 per cent of patients with high blood pressure, plasma renin was below the level seen in subjects with lower blood pressure. This has led many to search for the mineralocorticoid that suppresses renin and I think it has proved like the search for the Holy Grail. The candidates have been aldosterone, 18-OH.DOC, DOC and other ster-

Table 6. Typical figures from a patient with Conn's syndrome due to a glomerulosa tumour of the adrenal cortex.

	Blood	Urine
Na	143 mEq/litre	100 mEq/litre
K	2.5 mEq/litre	60 mEq/litre
HCO_3	32 mEq/litre	
Plasma renin	20 pg/ml/hr (100-1000)	
Plasma aldosterone	30 ng/100 ml (5-15)	

oids[91, 92]. Despite the emphasis on aldosterone provided by the work of Genest and his colleagues[93], most would implicate it rarely. I believe that even the syndrome of bilateral adrenal hyperplasia with low renin[94, 95] becomes easier to differentiate if a renin assay that can measure the very low levels usually seen with Conn's syndrome is used, since the former usually has a higher renin value. The other major mineralocorticoid, 18-OH.DOC, does not seem to be biologically very active and certainly does not correlate very well with blood pressure. Occasional examples of excess of DOC may be seen but they are extremely rare[96] and other supposed steroid 'syndromes' have been put forward, only to falter for lack of support. The definition of a low renin group may in itself be too arbitrary, as has been pointed out by Swales *et al.*[97], who found a continuous distribution without any suggestion of a division into distinct populations. It is, however, very difficult to rule out more than one population if the percentage of the total is low. This would, after all, apply to the group with a tumour in the adrenal cortex and they are defined by finding different aldosterone responses to various stimuli such as posture and diuretics. It seems quite clear that there is a group of subjects with very low renin who are relatively resistant to elevation of plasma renin activity by the usual stimuli[98].

Environmental Stimuli on a Strong Genetic Background

If we accept the strong genetic background in hypertension, then it may be, as has been suggested before, that various environmental influences activate it.

Social Stresses

In this context I am using the word stress as meaning an influence that makes the subject feel uncomfortable or unhappy. There have been many studies of groups living under difficult conditions, aimed at defining the importance of social stress in raising blood pressure; for example, a comparison was made between the blood pressure of black populations living in the inner city ghettoes versus those living in pleasanter suburbs[99]. A difference in the mean blood pressure for the groups was discovered but there are inevitable flaws in this type of approach since what the epidemiologists call 'confounding factors' always enter. Put another way, the reason some people live in the inner city may be because there are already differences of intelligence or physique which mean they will be subject to the supposed greater misery of life in the inner city because they have no economic alternative. This sort of influence is easier to arrange in experimental animals, and segregation in one group of spontaneously hypertensive rats leads to a lower blood pressure[100]. These rats are hypermotile, so this finding perhaps merely confirms that irritating colleagues are likely to elevate the blood pressure of others. In another human situation of considerable interest, those who confidently forecast that being incorporated into a trial for the treatment of hypertension[101] and being allocated to either a treated or control group receiving a placebo would cause undue anxiety were proved completely wrong. The study by Mann[102] showed that those within the trial had fewer neurotic symptoms than those who were excluded because their blood pressure was normal. There was no substitute for trying to measure the effects of a stimulus, and the use of the word stress, which always seems to be used in an adverse sense, could well be abandoned, since it is a dubious word and I am sure leads to suspension of clear thought and definition of the stimulus.

Alcohol

A number of studies of the effects of alcohol on blood pressure, most being cross-sectional studies, have shown heavier drinkers to have higher blood pressures[103]. The cohort of American naval pilots already referred to yielded other interesting information. Not only were those with higher blood pressures heavier, but they also drank more alcohol[11]. Of course, this does not prove that excess alcohol causes hypertension, merely that it is commonly associated with it. There is a less strong association in the Framingham studies[104] and a stronger one in those from Glasgow[105]. Proper account has to be taken of other differences between Framingham and Glasgow which might require diplomacy in scientific assessment. A further interesting Glaswegian observation was that, as in other vascular disease, smoking was more common in those developing malignant hypertension and particularly in those who ended up with severe renal failure[106].

The Contraceptive Pill

There has been controversy and lack of uniformity about data in relation to the contraceptive pill[107-109]. In a well-controlled prospective study Weir and his colleagues[110] showed that in a small group a pill consisting of an oestrogen and a progestogen raised the blood pressure uniformly compared with a group using other contraceptive means. The rise was not very great but it was definite and, of course, there are some women whose blood pressure may reach alarming and even malignant levels. Another important study showed that, even among those whose pressure dropped initially when taken off the contraceptive pill, there were some whose pressure had crept up again when re-examined months later[111]. Aber and his colleagues[112] suggested that there is a group of hypertensive women who have suffered renal damage, with glomerular and vascular changes. While this must represent a very small percentage among the large numbers of women on the pill, it has to be borne in mind as a possibility when looking at women referred because of a raised pressure. The link between familial hypertension and hypertension in pregnancy in this group of women is still uncertain.

Pregnancy

The possible behaviour of the blood pressure in preg-

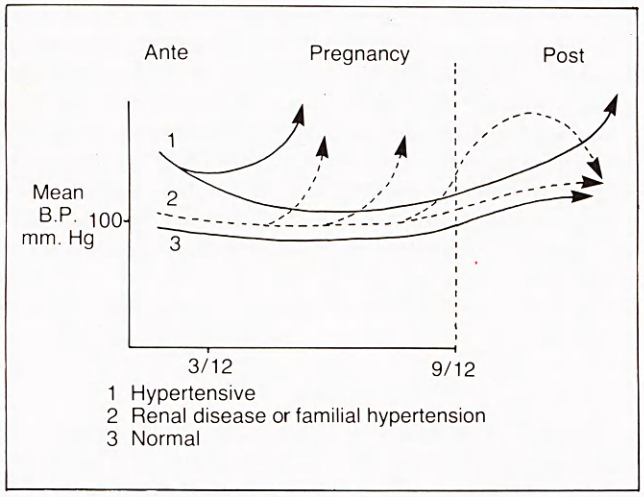

Fig. 6. *The possible pathways for blood pressure before, during and after pregnancy in different groups of subjects, showing the possibility of confusion in attributing any particular cause on the basis of too little knowledge about the total pattern in any one individual.*

nancy is shown in Fig. 6 and the various categories are of great importance in offering insights into hypertension[113, 114]. My own experience suggests that the patient with established hypertension of unknown cause may occasionally drop her blood pressure in early pregnancy and go the whole way through pregnancy without any trouble, the blood pressure rising again in the post-partum period. At one time these women were regarded as having renal disease of pregnancy or in some cases post-partum eclampsia, since their previous blood pressures were not known. I have followed several women through a number of pregnancies and have verified this behaviour. They can at any time, even from early in pregnancy, raise their blood pressure abruptly and the pregnancy is terminated with a dead fetus. Normal blood pressure lowers gently at about the third month, to rise equally gently towards the end of pregnancy. The most interesting and common group are those whose hypertension is essential or has an underlying renal cause. Their blood pressure may behave similarly during pregnancy. Women with a renal cause of hypertension may go through the pregnancy without trouble, but their blood pressure may rise at any time from the third month onwards, to return to a normal level post-partum. The same pattern may be followed by those with essential familial hypertension. However, the usual pattern is for the rise of pressure to be seen only in the last trimester and to be relatively mild. This pattern is repeated in successive pregnancies, often with the blood pressure getting higher each time, yet still returning to much the same sort of level between pregnancies. About half of these women present in their forties with undoubted hypertension and show a strong family history of high blood pressure. What happens in pregnancy to raise the pressure is unknown, but in this group the plasma renin activity and aldosterone are less than in normal pregnancy[115, 116]. Pregnancy must still offer the biggest clue to the basic faults in essential hypertension, since, in contrast, from a population study in South Wales, Miall[117] found a negative correlation between multiparity and blood pressure.

Salt

The relation of sodium chloride to high blood pressure has a venerable tradition which is an indication of the doubts surrounding the subject. The list of names, Ambard and Beaujard (1904), Allen (1920), Kempner (1944), Dahl (1958), Meneely (1958), Denton (1965), gives some indication of those most active in assigning an important role to an excess of sodium chloride in the diet (*see* Denton[118], Knudsen *et al.*[119] and Meneely and Battarbee[120] for references). Cross-sectional studies of populations have shown a poor correlation of blood pressure with sodium intake, so perhaps the most important concept to arise has been that of Dahl, using experimental animals, and then widening the argument to the human condition. He bred out from a common strain of rats two types named salt sensitive and salt resistant. The first group readily elevated their blood pressure with a heavy intake of sodium chloride; the others were resistant. They could be bred true, and if they were exposed to salt from an early age and then put on a low salt diet, it seemed that the damage had been done, since the blood pressure then rose in the same fashion as if salt had been maintained throughout. From this Dahl argued that if the human state were the same, only an appropriate percentage of the population would raise their blood pressures when exposed to high salt and this would be the perfect example of an environmental influence on a strong genetic background. He further pointed out that babies' milk products in the USA contain a large amount of sodium chloride, put there by the manufacturers because the mothers liked the taste better than saltless products. If this concept is allied to data which show that populations in different parts of the world taking very little salt have much lower blood pressures than those taking a lot of salt, the case would seem to be made[121]. In Dahl's view, the difficulties of lowering blood pressure by decreasing the salt intake would not necessarily be relevant since the effect of salt in the salt sensitive strain of rats appeared almost like an induction system in the early years of life. Prospective cohort studies are the most desirable approach but bristle with difficulty in our sorts of society.

Race and Environment

In some ways the biggest changes in environment in similar groups of the population have been observed in those races moving from a rural to an urban life. Shaper[122] showed that recruits to the Kenyan Army raised their blood pressure considerably while at the same time increasing their body weight. It has to be stressed that far more than salt intake is increased with this kind of transition, and calorie intake could be important. This sort of study needs widening while there is still the opportunity in areas like Africa. However, are there other racial differences? The most obvious are those that have

been established between what may be broadly termed black and white populations. A recent local study[38, 39] in a factory employing black and white workers with similar social, financial and dietary backgrounds, is of interest. The black workers had a mean blood pressure that was higher and significantly skewed to the right. This was allied to a plasma renin activity with a much higher percentage of very low values in the black population. There was no difference in plasma noradrenaline values, plasma aldosterone level or urinary sodium between black and white. In a group of black patients with definite raised blood pressure, seen at St Mary's Hospital the number with plasma renin activity that was very low, in the Conn's tumour range if seen in whites, was very high, but all in this group had normal plasma aldosterone. This is a common finding. Urinary kallikrein is also lower in blacks than whites[123] but the reason for these findings is not clear. It may be an ethnic variation that has no particular functional significance.

Therapeutic Classification

The major points of attack for the drugs used in the treatment of hypertension are shown in Fig. 7. The emphasis on the central and sympathetic nervous system is obvious and reminds me that when the first major drug, hexamethonium, was introduced by Paton and Zaimis in 1949[124], Paton expressed the hope that this

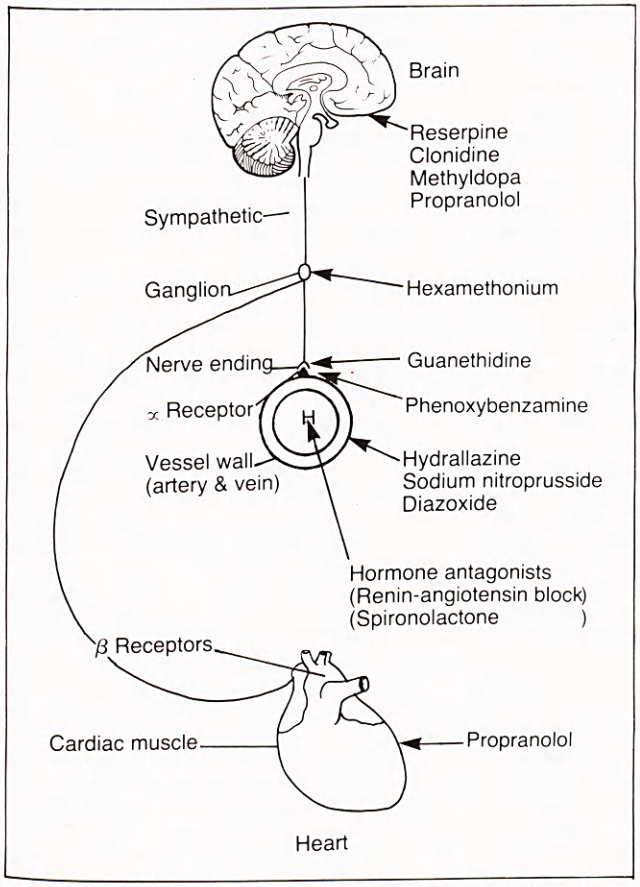

Fig. 7. *The main sites of action of some of the drugs that have been used in the treatment of high blood pressure.*

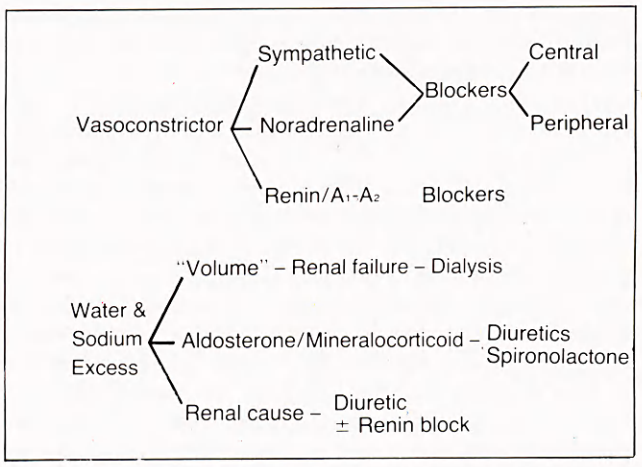

Fig. 8[69]. *The simple basic concept usually advanced to support a therapeutic classification of hypertension, leading to the use of sympathetic, catecholamine and renin/angiotensin blocking agents, on the one hand, and substances that reduce extracellular water and sodium, on the other.*

ganglion blocker would enable us to define the real role of the sympathetic nervous system in hypertension. A reasonable hope, but nearly 30 years later full realisation is still awaited. The problem is to quantify precisely the sympathetic nerve activity, using plasma levels of noradrenaline. However, real progress is being made. The therapeutic approach has been dominated in the last few years by the so-called 'vasoconstrictor versus volume' concept propounded by Laragh *et al.*[125] and diagrammatically represented in slightly extended form in Fig. 8. He based his argument on the idea that those who responded to a beta blocker like propranolol with an effective fall in blood pressure were those with the predominant angiotensin vasoconstriction, while those who responded to a diuretic like hydrochlorothiazide showed a dependence on volume and perhaps sodium and had a lower plasma renin activity. In between these extremes was a heterogeneous collection of patients with different proportions of vasoconstrictor/volume factors.

The difficulty with this concept is that propranolol has numerous actions in the brain and heart, as well as on the release of renin[126]. It has been shown that in many subjects inhibition of renin release occurs before blood pressure is affected[127]. From the other point of view, even though there would be support for the concept that thiazides and other diuretics do lower the blood pressure of subjects with low plasma renin activity, they will also lower the pressure of those with normal or even high plasma renin activity. A recent study by Swales *et al.*[97], using a double blind approach, did not support the specific properties of either propranolol or thiazide in relation to plasma renin activity. Furthermore, the way in which a thiazide lowers the blood pressure is not clear[128], and to equate such a lowering with an effect on some volume that is relevant to the blood pressure, such as plasma volume, needs support by measurements in the groups under consideration, e.g. low or high renin[129].

A different therapeutic approach has been employed using blockade of the renin-angiotensin system and among the methods available three have been seriously used in man. The first was competitive blockade using a synthetic analogue of angiotensin II in which the substitution is sarcosine at the N terminus and alanine at the C terminus[130, 131]. The biological activity of angiotensin depends heavily on the integrity of phenylalanine at the C terminus, and the presence of sarcosine seems to prolong the action, perhaps by lessened destruction *in vivo*. Though the analogue is an excellent blocker of angiotensin II, it does have agonist properties of its own, especially on the kidney[132], where its vasoconstrictor action depends on the integrity of the sympathetic nerves[133]. Nevertheless, it does seem to lower the blood pressure in proportion to the pressor effect of angiotensin II in the circulation[69].

The next approach was by inhibition of converting enzyme. Two main substances have been used in man. The first is a peptide derived from snake venom (Bothrops jararaca)[134-136]. The second is the result of a most elegant piece of chemistry in which D3-mercapto-2-methyl-propranolol-1-proline (captopril) was synthesised by Ondetti *et al.*[137] and shown to block the active site of the zinc-containing enzyme. Converting enzyme is also responsible for bradykinin destruction, so the use of either of these substances could potentially produce effects by maintaining higher levels of bradykinin in the circulation and other tissues. In short, there was lack of specificity with both these agents. The latter drug is effective by mouth in contrast to the former, and already many reports have appeared showing its effectiveness in lowering the pressure[85, 138]. As with saralasin, there seems to be a relationship with the plasma renin activity. The full range of activities of captopril are being investigated but no doubt the same problems of specificity will arise and already it seems clear that the blood pressure may be lowered in patients in whom levels of plasma renin activity are not high[85].

A large-scale randomised therapeutic trial in hypertension offered a chance to see effects without selection or prejudice[101]. The placebo effect was quite considerable and only after a few years did the mean pressure for the untreated group show a significant rise. The mean drop in pressure was the same whether propranolol or thiazide were being considered, and as about 75 per cent of each group is still treated with a single drug, it suggests that there is not a great deal of specificity in the response to either drug. The therapeutic approach to classification therefore requires great care.

Conclusion

In all this discussion of the various concepts relating to high blood pressure there are, I believe, a number of stable reference points about which there can be little argument. Therefore I believe they should always be kept to the forefront in discussions on the nature of high blood pressure. The first is that the cardiac output is usually not raised and may often be less than expected. The second is that plasma volume measured as ^{131}I albumin space is most commonly lower than in those with a lower blood pressure. Finally, after all the discussion of raised cardiac output and excessive volume, I keep my eye firmly on the increased peripheral resistance that is a cardinal feature of all cases of persistently elevated blood pressure, and I therefore believe that the mechanisms of what is at present essential hypertension will be found among those in which the major effect is an elevation in peripheral resistance.

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