Current theories of arterial hypertension have a relatively short history and are still undergoing drastic revision. The purpose of this very brief retrospective review is to show how great the changes in theory have been since we wrote "A Guide to the Theory of Arterial Hypertension" (1) 15 years ago and to highlight some of my many biases. Documentation is spotty and far from comprehensive, it fails to confer priority ratings, and it reflects my age. The review is chiefly directed at young investigators as a reminder that they have an intellectual past, often worth knowing.

Bright (1827), Gull and Sutton (1872), Mahomed (1879), Huchard (1889), and Albutt (1895) laid some sound clinical groundwork in the field of arterial hypertension, but they also sowed etiologic confusion. Many clinicians believed, for instance, that elevated blood pressure forced blood through thickened arteries and arterioles, thus ensuring adequate perfusion of tissues. Consequently, they thought that the reduction of blood pressure could only be detrimental.

With the modern era, several fundamental problems arose. (1) Did cardiovascular disease precede or follow the occurrence of hypertension? (2) Was the rise in blood pressure in essential hypertension due to a single cause? (3) If so, was the kidney, the nervous system, the endocrine system, or the hemodynamic changes in the heart and blood vessels the stimulus for the rise in blood pressure? (4) Was lowering blood pressure harmful or desirable? (5) What were the exact sequences of hemodynamic change which resulted in chronic hypertension? It is around all these fundamental questions that the extraordinarily productive work of the past four decades has circled.

NEURAL MECHANISMS

Both Prinzmetal and Wilson (2) and Pickering (3) measured blood flow through the forearm, including muscle and skin, and found similar rates in normal subjects and subjects with essential hypertension at rest and after the strong dilator stimulus provided by 10 minutes of circulatory arrest. In addition Prinzmetal and Wilson (2) found similar flow rates in both groups of subjects in response to local heating induced by warming the body and injecting Novocaine around the cervicodorsal sympathetic ganglia. Pickering (3) also showed that heating the body abolished sympathetic tone from the vessels of the hand, although blood flow remained the same in normal and hypertensive subjects. These vessels seemed to be narrowed in the hypertensive subjects by a nonneural agent. Pickering (4) later noted that these observations were largely of historical interest, because flow measurements without previous arrest of the circulation to the hand represent mixed hand and forearm flows and because two tissues, i.e., muscle and skin, were involved. Later, others found that blood flow was higher in skeletal muscle and lower in the kidneys of some hypertensive subjects than it was in normal subjects.

Both of these studies created controversy as well as widespread interest, and they greatly dampened the ardor of those who held that the nervous system was important in either the initiation or the maintenance of hypertension. The latter view was based on the fact that severe hypertension could be produced in dogs by cutting the buffer nerves and that a patient's blood pressure could respond to emotional stimuli.

As knowledge accumulated, it became increasingly evident that the nervous system was indeed very much involved in hypertension. The early studies of the fall in blood pressure resulting from extensive sympathectomy and from administration of ganglionic blocking agents could not be lightly dismissed. In the period beginning about 1950, many drugs which act strongly on components of the nervous system proved to be highly effective in the treatment of essential and malignant hypertension.
Another mechanism involving neural regulation which called attention to the problem of maintaining tissue perfusion by feedback was the "resetting phenomenon" observed in experimental renal hypertension. When pressure rises within a few days after hypertension is induced, the mechanoreceptors of the carotid sinus reset themselves to maintain rather than to suppress the elevated arterial blood pressure. Buffering no longer helps to maintain normal pressure. Some believe that resetting is demonstrable in patients with established essential hypertension. Aars (5) attributes the resetting to structural changes in the arterial wall of the sinus rather than to changes in its nerve endings; the evidence is inconclusive.

HUMORAL MECHANISMS

Goldblatt et al. (6) strongly influenced thinking about the role of humoral mechanisms in hypertension by demonstrating that persistent hypertension could be produced by constricting the renal arteries. They vigorously espoused the view that essential hypertension was due figuratively to a myriad of tiny clips on the renal vessels causing liberation of a humoral pressor agent. This hypothesis opened the way to clearer definition and treatment of renovascular hypertension in man but failed to explain essential hypertension satisfactorily.

With the discovery of angiotensin by Braun-Menédez et al. (7) and by Page and Helmer (8) followed by its synthesis by Bumpus et al. (9) and Schwyzer et al. (10), a new chapter in humoral mechanisms began, leading to many unexpected findings of clinical usefulness and theoretical interest in addition to an enormous literature. But angiotensin did not fully explain in simple fashion either essential or renovascular hypertension as had been hoped, although a close connection with the latter became well established and the association with essential hypertension was tantalizing. Severe hypertension due to renin-producing tumors of the juxtaglomerular body have been found. In most patients with other forms of hypertension, not enough angiotensin is formed to maintain elevated pressure, unless there are indirect actions involving the nervous system or changes in the chemical environment associated with smooth muscle contraction of arterioles which increased the muscle's responsiveness.

There have been major advances in the understanding of the many components of the humoral system. The mechanisms of action of angiotensin have proved to be vastly more complicated than anticipated. It has both a central and a peripheral action, and the enzyme system for the synthesis of angiotensin has been found in the brain as well as in the kidneys.

A variety of blocking agents has been developed for the proteolytic enzyme which converts the vascular inactive angiotensin I to the octapeptide angiotensin II: a series of competitive peptides and antiangiotensin immune bodies has also been developed. As might have been suspected with such important but complicated tools, the results until recently have been discordant. Recent work in which peptide blocking agents have been synthesized both to prevent conversion of angiotensin I to angiotensin II and to compete for the vascular action of angiotensin II has now demonstrated that such blockade lowers arterial blood pressure in both experimental acute and chronic renal hypertension and possibly in essential hypertension. This result was unexpected, since most investigators had tentatively accepted the view that angiotensin was important in the genesis of acute hypertension but was unimportant in the maintenance of hypertension. Pursuit of this topic is currently leading to a profusion of results.

Much the same problem must be faced with the development of aldosterone antagonists such as spironolactone. Spironolactone reduces blood pressure to normal in some patients with essential hypertension but not in others. Does this mean that in a group of hypertensive patients aldosterone is actively participating in the maintenance of hypertension in some but not in others? According to Dustan, those patients in whom the hypertension is chiefly volume dependent respond best to spironolactone. Indeed, they also respond best to thiazide diuretics.

Further complicating the humoral picture have been the somewhat vague suggestions and uncertain evidence that some of the prostaglandins may be involved in the humoral mechanisms of hypertension. Although most evidence suggests that the catecholamines are the chief neurotransmitters, so far no one has discovered a specific defect in their metabolism which characterizes hypertension, despite the fact that blockade of neural transmission has a profound effect on blood pressure level. Furthermore, norepinephrine may participate in the control of renin release.

Currently, it is possible only to guess how humoral agents such as bradykinin and prostaglandins might be involved in the mechanisms of hypertension. Indeed, it is quite possible that there are...
other as yet unrecognized agents concerned with stimulation of cardiovascular structural changes and the maintenance of vasoconstriction. Some believe that during the chronic phase of hypertension equilibrated systems of agonists are constantly at work, but others view the chronic phase as an interim plateau in which a new steady state has been achieved.

Finally, much evidence, experimental and clinical, has accumulated to prove the importance of the adrenal glands, especially the cortex, in the mechanisms of hypertension.

**ADRENAL-ELECTROLYTE MECHANISMS**

The importance of salt-water metabolism, adrenal corticoids, and their control by the kidneys was formulated by Masson et al. (11) on the basis of the demonstration by Deane and Masson (12) of the hypertrophy of the adrenal zona glomerulosa resulting from administration of renin and angiotensin. However, they did not pursue the matter when sufficient quantities of angiotensin became available to put the concept to a more definitive analysis.

That the secretion of aldosterone is to an important degree dependent on the level of plasma angiotensin II has been shown by the skilled experiments of Davis et al. (13), Genest et al. (14), and Laragh et al. (15).

There is little doubt that in many kinds of hypertension other than essential, these factors are importantly involved. Indeed, some believe they are also concerned in the genesis and maintenance of elevated pressure in essential hypertension. Excess secretion of aldosterone by the adrenal cortical adenoma proved the potentiality of the adrenal cortex to elicit chronic arterial hypertension.

This aspect of the genesis of essential hypertension has become increasingly important because of the clinical use of aldosterone antagonists such as spironolactone. Growing evidence suggests that some subjects with essential hypertension differ from others in that they have a low level of plasma renin activity and a normal secretory rate of aldosterone. The classification of essential hypertension as to high or low levels of plasma renin activity is a subject currently under excited discussion. Brown et al. (16) and many others began treating hypertensive patients with spironolactone, and since then it has been shown that best results are obtained in those with low plasma renin levels without hyperaldosteronism. The most recent work of Brown et al. points to the effectiveness of spironolactone even when aldosterone is elevated if plasma renin activity is low. Here again, plasma and extracellular fluid volume are often critical determinants of the level of the blood pressure as emphasized by Dustan et al. (40).

Currently the work of Melby et al. (17) has aroused much interest and speculation on the possible participation of another mineralocorticoid that might be secreted in patients with low-renin hypertension. The adrenal vein effluent was shown to contain substantial amounts of 18-OH-deoxycorticosterone (DOC), and the amount is increased in experimental hypertension. The regulation of this hormone is adrenocorticotropic hormone (ACTH) dependent; hence, suppression of ACTH secretion by dexamethasone in patients with low-renin hypertension and increased 18-OH-DOC causes a sharp fall in the steroid and the restoration of normal blood pressure. But this explanation is a very partial answer, because secretion of 18-OH-DOC is elevated in only a small percent of subjects with low-renin hypertension and, furthermore, this steroid is a relatively weak mineralocorticoid. Resolution of this complex problem will certainly result from the work now in progress in several laboratories.

Perusal of the vast literature on adrenal participation in secondary hypertension leaves no doubt of its importance. Much less impressive is the development of the problem of its abnormal involvement in essential hypertension. It must be evident to the reader that a large sector of modern thinking about this problem has deliberately been omitted.

**STRUCTURAL MECHANISMS**

About two decades ago, Folkow et al. (18) began a series of important experiments to verify much older conclusions that thickening of arteriolar muscle, in particular, occurs in chronic hypertension along with left ventricular hypertrophy. They also suggested that the increased peripheral resistance so induced was widespread and occurred within days of an intermittent increase in cardiac output which they accepted as a critical factor in initiating hypertension.

Folkow et al. (19) have now taken the position that essential hypertension is triggered by intermittent bouts of hypothalamic neurohumoral stimulation which increase cardiac output in genetically predisposed persons. In turn, the increased blood flow so produced is countered by increased peripheral resistance which occurs within days in rats and within an unknown time in man. The lumens of the resistance vessels are encroached on by medial hy-
hypertrophy. Folkow suggests that if the arterial blood pressure is reduced, these structural changes in the resistance vessels disappear.

Folkow makes a good case for such generalized structural change in resistance vessels as the mechanism by which peripheral resistance is maintained. The medial hypertrophy of these vessels seems closely related to the pressure load, although there are exceptions which occur in other diseases in which hypertrophy is seen, at least in special areas, without hypertension. If this is so, then even during maximal vasodilatation regional flow resistance would be higher than normal.

A question may be raised as to what constitutes and effects "maximal dilatation." Folkow uses the term "medial hypertrophy" to denote an absolute increase in smooth muscle volume, and he uses "wall thickness" in a relative sense to indicate a structurally increased ratio between thickness and internal radius. This relative increase has been recognized in hypertension for many years. He attributes the "hyperreactivity" of essential hypertension to structural change. It should, however, be remembered that the problem of cardiovascular hypersensitivity in essential hypertension is far from an established fact. Folkow also attributes the baroreceptor resetting phenomenon to structural adaptation.

There seems to be some confusion in the minds of the experts as to precisely how Folkow envisions the triggering mechanism for initiating hypertension. Actually he is very explicit. The change in bulk and design of the smooth muscle results from changes in functional demand. But an intermittent pressure rise constitutes the demand. Such functional loads are unlikely to originate in the kidneys; hence, he invokes the hypothalamic defense area which responds to the variety of psychogenic stimuli in daily life. He states that "... essential hypertension might be the result of a complex interaction between the centrally elicited pressure and output increases and a gradual structural adaptive response of heart and precapillary vessels if the pressor responses were repeated for a sufficient period of time." This theory has much in its favor. Since it is of such significance, it demands the most searching analysis of the evidence supporting and opposing it. The following only suggests a general outline of current thinking.

Most of the critical experiments, but not all, have been done in rats, an animal especially susceptible to structural vascular change and production of hypertension, and in the recently developed strains of rats that are highly susceptible to spontaneous hypertension. It has been claimed that weak and repeated stimulation of the hypothalamic defense areas by implanted electrodes produces persistent hypertension in mice, rats, and monkeys, as does operant conditioning. The evidence for maintained hypertension published to date is not convincing. Definitive evidence must come from further study.

The problem of the rapidity and kind of structural changes that occur in the heart and resistance vessels in the initial phase of hypertension is an exceedingly difficult one to solve. Reduction of arterial blood pressure in patients with essential hypertension, and especially those with the malignant variety, leads to reduced heart size and improves the patient's prognosis, as was shown many years ago during the days of extensive lumbodorsal sympathectomy. In animals with renovascular hypertension both the size and the weight of the heart are reduced by treatment, and the vascular lesions tend to heal even when the hypertension is malignant. There appears to be a direct relationship between the systolic pressure and the medial thickening.

It is difficult to explain why the development of hypertension and medial hypertrophy does not occur in many patients with increased cardiac output, such as those with hyperdynamic circulation, marked nutritional anemia, hyperthyroidism, and Paget's disease. Even patients with severe paroxysmal hypertension due to pheochromocytoma often have normal pressure between bouts of their illness.

If structural change is as "irreversibly" advanced as it appears to the pathologist, then why is blood pressure so readily reduced and tissue perfusion unaltered in most patients with severe chronic hypertension when the proper treatment is given? That structural change causes inability of blood vessels to dilate fully has been repeatedly shown. It is hard to believe that peripheral resistance is lowered by quick restructuring of such thickened blood vessels.

The question of how the structural changes occur so rapidly, even with mild and intermittent increases in cardiac output, is largely unstudied. Indeed, the evidence for such changes is meager. Why some persons with such gentle urging as a small (20%) increase in cardiac output will respond with persistent hypertension as an adaptation whereas most others will not is obscure. If they did so, it would surely be classified as a maladaptation.
Such an adaptive response demonstrates the potential "unwisdom" of the body which may end in catastrophe, since most people are regularly exposed to noxious neurohumoral stimuli of very considerable intensity along with relatively large increases in cardiac output. Perhaps the genetic factor is not present, although this seems too facile an explanation.

A FEW HEMODYNAMIC CONSIDERATIONS

Until several years ago the hemodynamics of hypertension of varied origin received relatively little attention. This neglect was in part due to the inadequacy of the measurements of cardiac output; momentary evaluation could be obtained, but even such measurement could not be made too often. With the introduction of implantable flowmeters a new dimension was introduced.

Early in the genesis of experimental renal hypertension, a moderate but transient increase in cardiac output has been noted; from this finding the view that the increased peripheral resistance is a result of stretch of the resistance vessels has been resurrected. Ledingham and Cohen (20) first vigorously promoted this concept, and their report on hypertensive rats has been confirmed and, I believe, their interpretation largely accepted. There are still some doubts in my mind as to whether this increase is of sufficient magnitude to set off the widespread increase in peripheral resistance without assists from as yet unrecognized sources.

Moderately increased cardiac output has been observed in the early stages of labile hypertension in a small number of patients who subsequently developed essential hypertension. Here again a generality has by no means been established, since the published measurements have often been within the limits of methodological error and even more importantly represent only momentary cardiac output. Not enough patients with increased output and labile hypertension have been followed long enough to determine whether chronic essential hypertension develops and in what proportion of such patients. I am convinced from my own experience from examining a group of young men in 1930 with labile hypertension that by no means all of them develop persistent hypertension. It should also be remembered that there is no substantial evidence that subjects with essential hypertension constitute a homogeneous population.

The clinical aspects of the hemodynamics of hypertension have been restudied and extended by a number of workers but especially by Frohlich et al. (21). They showed in hypertensive patients that extracellular fluid volume was often related to diastolic pressure. Plasma volume was reduced in both essential and renovascular hypertension, possibly reflecting altered capillary filtering force, because total extracellular fluid volume was normal. Drug treatments modified conditions so that diastolic pressure became a direct function of plasma volume; hence, good blood pressure control depended on maintaining a reduced plasma volume.

THE ATHEROGENIC PROPENSITY OF HYPERTENSION

For many years clinicians recognized that atherosclerosis and its complications commonly accompanied hypertension. Since no way was available to prevent or treat atherosclerosis, it was accepted as inevitable. But after the introduction of potent antihypertensive agents nearly 24 years ago, it became possible to determine whether these atherosclerotic complications could be reduced by reducing arterial blood pressure.

The first study of this kind was that of Corcoran et al. (22) in 1956, in which it was shown that the complications of atherosclerosis are more common in patients who do not respond well to antihypertensive treatment. The severity of the hypertension was a major factor in the atherogenesis of hypertension. Their data strongly suggested that prompt, effective treatment of hypertensive disease was the best means of preventing atherosclerotic complications.

The adequate treatment of malignant hypertension, as was shown during the heyday of sympathectomy, proved the most dramatic example of the value of reducing blood pressure. Renal biopsy specimens showed clear evidence of healing of the necrotizing vascular lesions. The mortality dropped sharply in the hands of everyone who treated the disease as a genuine medical emergency by use of sodium nitroprusside and, later, diazoxide.

It has taken about 15 years for many physicians and the public to realize the dangers and the significance of chronic hypertension despite the clear evidence from insurance statistics. Such an incubation period, however, is a common occurrence in the application of discovery.

There are three broad aspects of the problem of atherogenicity which often unconsciously become blurred: (1) atherogenesis, (2) hypertensive thickening of small resistance vessels, and (3) necrotizing, hemorrhagic arteriolitis.

The first of these, atherogenesis in hypertensive patients, has received no clearer answer than
atherogenesis in *nonhypertensive* patients. What has become clear is that if hypertensive disease is to be fully treated in large populations, concurrent treatment or prevention of atherogenesis is necessary. It is generally believed that the hypertrophic changes in resistance vessels will at least not advance if hypertension is controlled. Little is known about the regulatory mechanism controlling this hypertrophy. The subject of the vascular changes in malignant hypertension became critical when it was recognized long ago in patients. Later somewhat similar changes were seen by Goldblatt in a few dogs with severe constriction of the renal artery. Then Byrom began his superb work on the vascular diseases of rats with renal hypertension which has extended through his career. He laid the foundation for an understanding of these interesting lesions which has only recently begun to be built on.

Atherogenesis and thrombogenesis are mechanisms which also lend themselves to reductive analysis using a mosaic framework, just as in hypertension (23).

**GENETIC SUSCEPTIBILITY**

There have been a number of distinguished contributions by investigators such as Platt (24), Thomas (25), Pickering (4), and Miall and Oldham (26) which leave little doubt about the heritability of essential hypertension. Thomas (27) has been the most persistent and effective student of this aspect of hypertension. The recent developments in experimental hypertension showing that strains of spontaneously hypertensive rats can be bred is of great importance. This trend began in earnest when Smirk, Dahl, and Okamoto demonstrated that genetically induced hypertension in rats could be reliably produced.

Smirk and Hall (28) and Okamoto and Aoki (29) have developed colonies of rats in which structural characteristics are genetically programed. In the meantime, Dahl et al. (30) have successfully bred rats that are supersensitive to the development of hypertension when they are fed salt. These contributions were all trenchant because it appears that the hemodynamics of these spontaneously hypertensive rats fairly closely resemble those in essential hypertension.

For practical reasons, genetic susceptibility to hypertension in human beings is usually not always determined or determinable. But such susceptibility may be a requisite part of the mechanism in some patients. In rats with spontaneous hypertension, central excitatory influences may indeed affect or initiate the elevation of blood pressure in those animals with a genetically programed hypertension but leave unaffected those without it. Folkow et al. state that "To all such alerting stimuli both young 'prehypertensive' and older spontaneously hypertensive rats with 'established' hypertension responded stronger than normotensive control rats in both pressure and heart rate."

Folkow is convinced from his studies of dose-response curves to vasoconstrictor agents using paired, constant-flow perfusion of isolated hindquarters from 7-month-old matched spontaneously hypertensive and normotensive rats that increased sensitivity to vasoconstrictor agents occurs in the vascular muscle of the hypertensive animals. The higher resistance and the increased response in the spontaneously hypertensive rats are due to enhanced maximal contractile strength per unit of medial muscle, hence to structural change. In spontaneously hypertensive rats, the characteristic hemodynamic changes of the resistance vessels must then be ascribed to an increase in the wall-lumen ratio. Folkow would abandon all current theories based on the assumption of the continuously raised vascular smooth muscle activity or tone to explain the chronically increased resistance in essential hypertension. This concept is denied by McGregor and Smirk (31) who found that the response of genetic and renal hypertensive rats to serotonin so greatly exceeds the hyperresponsiveness to angiotensin and norepinephrine that a structural change in the vessels is unreasonable.

In a report on a recent conference edited by Professor Okamoto (32) the similarity of essential hypertension to the disease in spontaneously hypertensive rats is well summarized. Some of the same problems involved in the theory of essential hypertension have arisen. For example, even though the experimental evidence shows either no increase or a decrease in sympathetic neural activity, blood pressure is brought to normal by the antihypertensive agents which have their primary action on the nervous system. Lowering blood pressure in hypertensive animals usually requires less depressor agent than is required in normotensive animals. If all essential and renal hypertension begins with an increase in cardiac output, then drugs such as propranolol, which lowers output, should be sovereign remedies that prevent the onset and cure the early phases of hypertension, but they are not! In human beings propranolol often is an effective antihypertensive drug in long-established hypertension.
So far, the relatively small amount of firm evidence suggests a close relationship between rats with spontaneous hypertension and those with essential hypertension but not an identity. The danger now lies in being either hypercritical or sanguine; time and good experiments will settle the matter.

If the view is accepted that hypertension is maintained by increased vascular resistance due to structural change of the blood vessels, then the main emphasis in research should be on the causes and mechanisms of this change. Increased sympathetic activity or pressor agents may only initiate the rise in pressure and the increase in cardiac output that trigger the autoregulation and augment peripheral resistance and medial hypertrophy. Since under this concept a pressure rise is the critical mechanism, treatment directed at reducing pressure should be valuable.

Although hypertension research has recently centered on spontaneously hypertensive rats, equally important is the work by Dahl (33) on purebred salt-sensitive rats. He has shown conclusively that in such rats hypertension and early death from vascular disease is salt dependent. A closer look at this interesting work will be omitted because it has repeatedly been reviewed. It is necessary to remember that Dahl makes a good case for the similarity of the disease in these rats to that of essential hypertension in human beings.

In any balanced study of the problem of hypertension sodium must weigh heavily.

COMPUTER ANALYSIS OF HEMODYNAMICS

In the past few years a valiant effort has been made by Guyton et al. (34) to apply computers to control systems analysis and modeling. In essence, Guyton et al. have tried to analyze mathematically much evidence that has been accumulating over the years. Unfortunately, in the early study of hypertension, methods were inadequate and the need for the most exacting experimental conditions was not appreciated.

Guyton believes that renovascular hypertension begins as a disturbance in renal function leading to retention of salt and water. This retention leads to increased cardiac output which in turn invokes a rise in arterial blood pressure and the response of "total body autoregulation." He concludes that arterial blood pressure cannot be elevated for long periods without (1) altering the function of the kidneys to change their output of water and electrolyte or (2) changing the intake of water and electrolytes. Factors such as autonomic reflexes, humoral agents, and structural change in resistance vessels play at most only transient roles. Although many investigators consider this concept simplistic, what Guyton has accomplished is to begin the application of mathematical analysis to this very complex problem.

Luetscher et al. (35) have presented another model of the human circulation regulated by the autonomic nervous system, angiotensin, and blood volume. This model allows them to classify essential hypertension into two groups: (1) that with increased autonomic activity, high plasma renin, low normal plasma volume, and high normal cardiac output and (2) that with increased exchangeable sodium, high normal plasma volume, subnormal plasma renin, and often impairment of autonomic function. The problem is still further complicated by the classification by Brunner et al. (36) into groups according to the plasma-renin levels in relation to sodium excretion.

THE MOSAIC THEORY

It appeared that none of the unitary theories—neural, humoral, endocrine, or structural—fully explained the mechanisms of essential hypertension. Each had proved helpful in understanding and diagnosing a variety of secondary types of hypertension due to renovascular disease, adrenal cortical adenomas, and pheochromocytomas. Still, good evidence was accumulating at such a rate that it seemed necessary to establish some more orderly structure onto which it could be fitted.

Page (37) in 1949 proposed what he called the "mosaic theory." It was based on the assumption that a steady state exists in the circulation in which the important regulatory factors are in equilibrium, maintaining blood pressure and tissue perfusion at relative constancy adapted to tissue needs. The diagram of Figure 1 illustrates what may be considered the most important regulatory factors working in an interrelated manner to control blood pressure. The extent to which these factors contribute to regulation of blood pressure may vary. This mosaic is not a rigid one, but instead it is comparable to the one in a kaleidoscope in which patterns can continuously change by merging into one another.

The diagram in Figure 1 is a two-dimensional attempt to portray an n-dimensional problem. It is somewhat analogous to the phase rule of J. Willard Gibbs, which is based on the postulate that the state of a system is determined by the number of phases and the mass of each phase. Despite the fact that innumerable properties can be ascribed to the
system, its state can be specified by the united number of variables which can be changed independently, together with the number of components making up the system. Although the relationships between the variables indicated in Figure 1 are well established in principle, the number of variables which can be changed in an independent manner to produce hypertension is not known, and therefore, the number, so to speak, of phases of hypertension (i.e., regulatory mechanisms) is not known.

Essential hypertension was designated "a disease of regulation" and no single unique underlying cause could be expected, except in secondary hypertension where one mechanism dominates all others. The concept of hypertension as a multifaceted or multifactorial disease was proposed not so much as an indication of complexity but as a postulate that there are several causes acting together. Whatever its demerits, the theory seemed to prevent research from becoming stultified.

THEORETICAL BASIS FOR THE INITIATION OF ESSENTIAL HYPERTENSION

There are three possible answers to the core problem of what initiates essential hypertension. (1) There is a single unknown mechanism which alone can start and maintain the elevation of blood pressure. Those who believe in this hypothesis find relatively little need for the mosaic theory. The regulation of blood pressure would then be analogous to pressure changes in a single-phase system where variables can be changed without altering one another. (2) There is a single triggering mechanism which becomes obscured when it is compensated for by change in other regulatory mechanisms. The obscured change might be viewed as being analogous to a two-phased system with one degree of freedom. (3) As proposed in the mosaic theory, there must be more than one alteration in the regulating system to override the many mechanisms of compensatory change.

The mosaic theory groups mechanisms without describing in detail the variables which operate as a single set in an interrelated manner. When I speak of "the humoral mechanisms" these comprise a great number of interreactions making it possible for them to function in the complex of the total body control of tissue perfusion. As an example, think of the problem confronting the body when the nervous system is surgically or chemically destroyed. Only three possible means are left to integrate the demands of each organ for its share of blood: the bloodstream, tissue conductance, and autoregulation.

I have proposed (38) that the bloodstream might act as a computer tape in which signals to organs are arranged in an integrated fashion. It is hard to conceive that the varied and powerful vasoactive substances enter into the circulation in a helter-skelter fashion. They must act relatedly to achieve chemical intercommunication to meet the changing needs of organs for blood. On the interconnecting band of blood must be printed the patterns giving directions for the responses of the heart and blood vessels. The term "integrated" would appear to be applicable to the bloodstream as well as to the nervous system.

The question might be raised whether the circulation can be considered a reversibly operating or even a closed system to analogize with thermodynamics. It can be considered analogous to the extent that steady states or equilibria exist. When the number of independently operating variables of essential hypertension are known, it is to be hoped that those subject to reversible change, which are genetically programed, will be controllable.

THEORY OF TREATMENT

If treatment is begun early, it might be anticipated that the vascular and myocardial changes would soon be reversed. Evidence from experimental renovascular hypertension suggests that this is true. Formerly, it was believed that when hypertension progressed into the "fixed" stage, antihypertensive therapy would be ineffective since the vascular changes were irreversible. My own
long experience with treatment of patients offers convincing evidence that this is not true. Page and Dusan (39) showed that after several years of treatment, many hypertensive patients have normal or nearly normal arterial blood pressure and less antihypertensive drugs are necessary to keep it so. Usually, the use of a thiazide diuretic sufficed. Whether vascular and myocardial restructuming occurred is not known but is a critical datum that should be obtained.

A second such datum is understanding of the neural mechanisms hypothesized as initiating the original increase in cardiac output and the rise in arterial blood pressure and peripheral resistance if, indeed, this is the hemodynamic sequence. Currently, it is only speculation, since no results so far have carried the necessary conviction for acceptance of this sequence. The humoral mechanisms and those concerned with water and electrolytes are beginning to be understood. But I stress only beginning, since the mechanism of action of substances such as angiotensin, prostaglandins, and serotonin have proved far more complex than was initially anticipated. For example, the peripheral actions of angiotensin may be blocked without affecting the central nervous ones. Lastly, the importance of salt and water metabolism and their effects on plasma volume are increasingly appreciated. It is ironic that one of the earliest subjects of concern in the treatment of hypertension at the turn of the century was none other than salt and water.

References


Brief Reviews: Arterial Hypertension in Retrospect
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Circ Res. 1974;34:133-142
doi: 10.1161/01.RES.34.2.133
Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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