THEORIES about the origin and development of hypertension, especially essential hypertension, blossom repeatedly and are as varied as the wild flowers on a mountain side and often as evanescent. Almost everyone of prominence in the field has yielded to the temptation, at least once, to offer an all or partly encompassing theory, only to have it marred by ever intrusive facts. I propose to discuss some of these theories or hypotheses point by point, and to try to indicate areas for future investigation likely to prove fruitful.

Page has suggested, on the basis of his vast experience in the field, that essential hypertension will prove to be not one disease, but many different diseases of different origin and development, all of which produce hypertension and its consequences in a kind of mosaic of causes, some of which may occur singly or together. This "Mosaic Theory," however, does not account for such things as hereditary predisposition and the interrelationships and dynamics of hypertensive disease. It also leaves about 85% of patients with hypertension still in the "essential" or "of unknown origin" category.

Pickering, however, addresses himself to the importance of the genetic factors. As in late onset diabetes, he believes that environmental factors must act on the hereditary substrate to produce clinical hypertension late in life and therefore perpetuate it; since like late onset diabetes, hypertension does not seem to interfere with procreation. The occurrence of hypertension in families must be carefully studied, separating factors transmitted by the chromosomes from those that are attributable to such factors as culture, diet, and other environmental impacts. Pickering, however, assigns only 25% of the rise in blood pressure to genetic and 75% to environmental factors. The exact nature of the genetic and environmental factors remains unclear.

Dahl and Freis attribute essential hypertension almost entirely to excessive ingestion of salt. This was and still is a rare commodity in many primitive societies and has become abundant in more advanced societies thus, it is thought, leading to the development of essential hypertension. Dahl et al. on the basis of his rat experiments, however, conceded that there must be hereditary substrates for hypertension to develop, but Freis cites the absence of hypertension in certain primitive societies where salt is scarce. The possibility of inbreeding and natural selection is not discussed.

Laragh et al. and others, on the other hand, on the basis of their work in man and in animals (particularly the two-kidney model, in which one renal artery is constricted, versus the one-kidney model, in which one kidney artery is constricted and the other kidney ablated) say that essential hypertension is either due to excessive retention of salt and water or to a high production of renin, angiotensin and aldosterone. They have not investigated genetic factors, as such, in human essential hypertension. It is possible that genetic factors, for example, contribute to plasma volume and/or endocrine mechanisms, but this has not been proven. These workers have, however, linked the mechanisms in part to the beta-receptors of the sympathetic nervous and adrenal medullary hormones, since propranolol seems to block the production of renin. The division of essential hypertension into high, normal and low renin classes has been subjected to persistent attack and counter attack but addresses only possible mechanisms and does not explain the origin of essential hypertension or what is primary and what is secondary.

The honored discoverer of Conn's syndrome or primary aldosteronism began to extend the idea of aldosteronism into the general field of essential hypertension. The postulated incidence of primary aldosteronism as a cause for essential hypertension gradually decreased over the years from 25% to less than 1%. Low renin hypertension was a particularly attractive target since endocrinologists including Genest, Melby et al. and Sennett et al. among others searched avidly, although largely unsuccessfully, for increased aldosterone or abnormal mineralcorticoids, which could be held up as causes
for at least some patients with essential hypertension. On the other side of the ledger, it soon became apparent that these steroids were either insufficient in quantity or too weak to produce the hypertension found, and that pseudo-primary hyperaldosteronism, as well as secondary hyperaldosteronism were results of, or participants in, the hypertensive process, since adrenal ablation in these conditions had little, if any, effect on the course of the severe hypertension in such patients.

One of the greatest success stories for the renin theory in hypertension came from the field of renovascular hypertension, explored by many initially, such as Howard et al. and Perera and Haelig, but expanded largely by Poutasie in Cleveland and Morris and DeBakey in Houston. It is interesting, here too, that their initial enthusiasm led these workers to suggest that 25% of essential hypertensive patients had these lesions and could be cured by surgery. The true figure, of course, is less than 5% and even here complete cure, with all the appropriate testing, is accomplished in only about one half of these cases, the rest requiring supplementary drug therapy. It is true, however, that the hypertension produced by renovascular obstruction is probably largely renin-mediated.

The biggest surgical success story is that for pheochromocytoma. If it is detected, and the biochemical urine tests are quite definitive, surgical removal results in cure of the hypertension in nearly all cases. Even here, there are flies in the ointment. Ten per cent of these tumors are malignant and require alphamethyl-tyrosine to block synthesis of the increased catecholamines produced. Some benign tumors are multi-focal, some occur in families, some have associated essential hypertension and others may remain undetected even by sophisticated biochemical testing. They may make parturition or incidental surgery highly hazardous. These cases, in total, however, comprise less than 1% of all the hypertensive population.

To complete the adrenal picture, Cushing's syndrome is often associated with hypertension, again comprising less than 1% of the cases, although some light has been thrown on its mechanisms. The blood vessels become more reactive to norepinephrine (NE), by either an increase in receptor sensitivity, or by increased activation of the post-receptor (second messenger) system, or of the contractile mechanism itself. There is also an increase in renin substrate and hence more angiotensin II elaborated.

Let us now return to the kidney which Goldblatt made such a likely candidate for originating most hypertension, including essential hypertension. Guyton, a physiologist, by studying the interrelationships between computerized black boxes representing various systems involved in hypertension, which he supported in part by experiment, concluded that only an abnormality causing prolonged autoregulation and a decrease in kidney function could produce sustained established hypertension. Again, this has been challenged and fought over, especially with reference to essential hypertension in man. The complexities of organ and cellular interaction always make physical and mathematical analogies suspect in biology, but the theory at present, cannot be definitively sustained or disproved.

There are also those who postulate a depressor effect of normal kidney, led at first by experiments performed by Hamilton and Grollman. Some of these depressor substances were identified as lipids (prostaglandins), polypeptides, proteins (medullary secretions), anti-renins or kinins and their precursors kallikreins. Abnormal amounts found in the urine and blood were cited as evidence that these substances or their relative absence might be the causes of essential hypertension. In fact, Lee et al. suggested that essential hypertension was caused by a decrease in prostaglandin A produced by impaired kidneys.

Prostaglandin E is largely destroyed by the lungs, but some may escape and be antagonistic to angiotensin II. In fact, increased reactivity to angiotensin II is one of the earliest hallmarks of toxemia of pregnancy and decreased prostaglandin E is postulated to be responsible for this. All this work remains to be adequately confirmed and interpreted, but one must not dismiss these possibilities out of hand.

There is also a "hemodynamic" theory supported particularly by Ledingham and Cohen. The argument goes something like this. Most hypertension begins with an increase in cardiac output, which in turn, increases pressure in the arterial tree. According to the Bayliss principle, this distention of the small arteries causes them to constrict, independent of nerve action, and the final increased peripheral resistance is produced in this way. The process of autoregulation whereby flow in an organ or a tissue is kept constant, regardless of variations in blood pressure, is a well-documented physiological principle, within limits. The only difficulty with this theory is that it fails to stand up in many patients with essential hypertension. Some patients have increases in cardiac output and never develop hypertension, as in anemia and even in some early hypertensive patients who never go on, despite increase in cardiac output, to develop full-fledged essential hypertension. They may even become normotensive. Also, some essential hypertensive patients do not go through the phase of increased cardiac output and develop increased peripheral resistance right from the start. In anemia or hyperthyroidism it may be argued that the vasodilating factors in the periphery overbalance the constricting Bayliss factor, but this argument cannot be used for the other cases cited. Another outgrowth of the hemodynamic theory is the fact that certain changes are found on the venous side of the circulation in early hypertension and in the pulmonary cardiac volume which indicate that early hypertension is neurally produced and is therefore of sympathetic nervous system origin.

The history of the baroreceptors in their relationship to hypertension is curious and begins in...
the early part of the century. Even as late as the 1930's there was controversy among physiologists as to whether respiration and blood pressure were controlled by direct stimulation of medullary centers or reflexly. The carotid sinus reflex was first discovered in Italy, and then made popular by Hering in Germany, and finally related to hypertension by Heymans and Neill in Belgium. More modern work on this subject continues and has frequently been led by Kezdi.

It was known for many years, however, that neurogenic hypertension could be produced in the dog by denervating the carotid and aortic baroreceptors. This hypertension is fluctuating and is associated with tachycardia. It is unlike the renovascular hypertension produced by Goldblatt in dogs, which took the center of the stage as resembling the kind of disease seen in human essential hypertension. It should be noted, however, that when Wakerlin et al. encased the carotid sinuses rigidly, thus preventing them from dilating, a fixed hypertension was produced very much like human essential hypertension.

In essential hypertension it is well established that the baroreceptors become "reset" at a higher level of blood pressure, although the exact physiological and biochemical reason for this is not clearly understood. If this were not so, there could be no hypertension, since baroreceptor activity would always bring the blood pressure down to normal. In physiological terms, this "resetting" simply means that the blood pressure threshold of stimulation of the baroreceptors is higher in hypertension and this is generally accepted to be true. The higher threshold, however, should be clearly distinguished from the sensitivity of these baroreceptors. Since lateral pressure is the stimulus, such sensitivity can be measured by the effect of changes in lateral pressure on heart rate or by measuring traffic over baroreceptor nerves with a given change in lateral pressure. A good deal of evidence has accumulated that a decrease in such sensitivity is produced more by the stiffness of the baroreceptor walls rather than by the hypertension itself. Thus, labile hypertension can be produced in animals by atherosclerosis alone and decreased nerve activity can be demonstrated in the baroreceptor nerves of these animals. Indirect evidence in man, using heart rate as the index of sensitivity to pressure change, also indicates that hypertension, per se, produces little, if any, difference from the normal, whereas hypertension associated with age and signs of atherosclerosis decreases baroreceptor sensitivity significantly.

Since the baroreceptor nerves are inhibitory to sympathetic outflow, this could, conceivably, contribute to labile hypertension in the aged along with other factors. There are two other well-known factors that produce hypertension de novo in the aged. The stiffness and lack of elasticity and enlargement of the arterial tree may produce an increase in systolic and a decrease in diastolic pressure. Also, if atherosclerosis affects the renal artery or arteries, renovascular hypertension may result. These are only the known complexities of hypertension in the aged and they may occur in any combination.

The baroreceptor inhibitory influences on the vasomotor center seem to be funneled through the tractus and nucleus solitarius and are mediated via epinephrine and norepinephrine. In fact, increased amounts of these catecholamines are found in the medullae of spontaneously hypertensive rats. Cutting the tractus solitarius stimulates the production of neuropeptide Y and stimulation of the nucleus solitarius produces release of epinephrine (E) and norepinephrine (NE) and hypotension. The effect of the higher brain centers on this mechanism are only now being studied, although susceptibility to anxiety and possibly anxiety itself and even psychosis increase plasma and urinary catecholamines, particularly E and possibly also increases responsiveness of the peripheral blood vessels to E, thus again producing so-called labile or borderline hypertension.

Speaking of "borderline" or labile hypertension, it should be stressed that all such hypertension does not necessarily progress to typical fixed essential hypertension with all its sequelae. Some cases revert to normotension and some may remain sporadic for years and never develop fixed hypertension. Lability is related more to increased excretion of E and reactivity to secreted E than NE and may exist together with fixed essential hypertension, which characteristically almost always displays increased responsiveness to NE, as well as to angiotensin II. The relationship of the E to the NE effect seems to be discrete and is not significantly correlated, but may be shown to be connected in some way in the future. There are, of course, some workers in Europe who consider central nervous system stimulation to be the "trigger" for the development of sustained essential hypertension, the increased reactivity of vascular smooth muscle in the latter being more on a structural than a biochemical basis but this has been refuted and is still extensively debated.

How much of this "trigger" factor is genetic and how much is environmental is still in question.

Attention was directed to the autonomic nervous system itself, first in the 1930's by surgeons like Peet, Grimson and Smithwick who removed various portions of the sympathetic nervous system and claimed cure of the disease. Some even combined such surgery with bilateral adrenalectomy to get rid of more catecholamine-producing tissue and perhaps for other reasons as well. This kind of surgery, however, was only used in the more advanced cases and was at most only partially successful. It was soon to be replaced by a variety of drugs that acted to reduce sympathetic nerve activity in many ways. Many, however, have inferred, from the effects of the surgery and of these drugs, that the sympathetic nervous system is involved in the etiology of essential hypertension. This has also been vigorously denied.

Increased sympathetic nerve discharge has been faulted as a cause for essential hypertension but has never been directly measured or proven electrophysiologically in man. The evidence for this rests on
the presence of increased catecholamines in the plasma of some one-third to one-half of essential hypertensive patients, as well on the demonstration of increased levels of dopamine-beta-hydroxylase (DBH) in the plasma, known to be a rough measure of sympathetic nerve discharge. Both of these assertions, however, have been refuted. One group of workers relates increased plasma levels of catecholamines to aging with no difference between normotensive and hypertensive groups. Plasma catecholamines have also been correlated with plasma renin activity (PRA). Other experimenters find DBH either normal or low in essential hypertensive patients. The effect of age is refuted by still another group, and there is evidence that mental as well as physical effort increases plasma and urinary catecholamines more in hypertensive than in normotensive subjects. It is noteworthy that excretion of catecholamine metabolites is normal in essential hypertensive subjects although fluctuations from the mean (standard deviation) is greater in the essential hypertensive population.

My group has also extended our work on reactivity into theory with at least two missteps. When we found that reactivity was increased fourfold in the digit in essential hypertension, we assumed this effect to be biochemical. We were aware of the reduction of the lumen of small blood vessels in essential hypertension and had described physiological evidence for this many years before, and attributed it to smooth muscle hypertrophy. But the increase in reactivity was too great and too easily and quickly changed by biochemical manipulation to be ascribed purely to structural factors. At about that time catechol O-methyl-transferase (COMT) was inferred by the findings of Armstrong et al. and described by Axelrod. We suggested that a deficiency of this enzyme (a protein) would explain our findings as well as the genetic factor (genes make proteins). We suggested this as a possible "cause" of essential hypertension. It soon became obvious from the study of urinary metabolites that COMT or other methylating enzymes work as well in essential hypertensive patients as in normotensive subjects.

Meanwhile, some of our workers found 1) a greater rate of decrease in plasma NE and its metabolites after infusion of tritiated NE in essential hypertension than normal; 2) a greater increase in the specific activity of a urinary metabolite of NE, normetanephrine (NM), after injection of a single bolus of tritiated NE; and 3) a greater increase in total urinary tritium excretion after injection of a tiny bolus of tritiated NE in essential hypertension than in normotensive subjects. Incidentally, if the dose was increased, the difference disappeared. We then postulated a decrease in sympathetic nerve uptake or re-uptake of NE as a major problem in essential hypertension, again implicating a protein, namely, that of the nerve cell synaptic membrane. This also proved to be probably incorrect since triyclic antidepressants do cause such a block and have no unusual effect on blood pressure. Also guanethidine and perhaps methyldopa causes such a block too, and these drugs depress rather than increase blood pressure.

To indicate how advances in theory help to improve therapy, however, concentration on vascular receptors and their cascades and on renin has promoted the use of combinations of both beta- and alpha-adrenergic blockers to treat essential hypertension. Instead of an alpha-adrenergic blocker, one may use a direct smooth muscle inhibitor such as hydralazine. Such a combination reduces blood pressure without orthostatic hypotension and only occasionally requires supplementation by a diuretic even in fairly severe hypertension. The production of renin is also known to be blocked by beta-receptor blockers such as propranolol, so that such therapy seems to be complementary, despite the large number of tablets sometimes needed. It points the direction that future research may take with profit to the patient.

One may now ask why it is that so much positive data in so many different systems have accumulated in the study of essential hypertension. This may be ascribed to several factors. In the first place, methods, especially in endocrinology and neuroendocrinology, have improved to such a fantastic extent that unbelievably small amounts of such hormones are now measurable in blood serum and urine. I need only cite radioimmunoassay, radioenzymatic assay, gas-liquid chromatography, mass spectroscopy and thin layer chromatography, in this respect. Since the hypertensions are a group of diseases that often extend over a lifetime, even though they may only become apparent in the third, fourth or fifth decades, many different systems of the body are involved and may be brought into play to initiate disease, or later to modify it. Our better methods now enable us to dissect out some of these factors, although, of course, not all.

Essential hypertension is not one disease. The effect of age and arteriosclerosis, for example, already outlined, may create or increase high blood pressure without any genetic blood pressure stimulus. The relationship of the initiation of hypertension by increased reactivity to E or NE or both remains to be clarified and its modification by prostaglandins and other antihypertensive substances is still obscure. It should be pointed out, however, that indomethacin, an inhibitor of prostaglandin synthesis, despite its ability to "cure" Bartter's syndrome, has little effect on blood pressure.

Also, the relationship between hereditary and environmental factors are still very poorly understood. What happens when someone born with a hypertensive trait develops chronic glomerulonephritis or is subject to severe emotional stress? It should be emphasized that no hypertensive patient is really like any other. Each is a unique combination of hereditary multigenic substrates, and varied environmental influences. This is why, among other reasons, therapy for the diseases called essential hypertension requires individualization rather than rigid formulation.
Summary

1. Various theories on the origin and development of hypertension offered over the years have been assessed critically.
2. It is concluded that no one theory is adequate at the present time to encompass all the known facts.
3. Continuously expanded understanding of hypertensive mechanisms, however, help in the individualization and therefore the improvement of various modalities of therapy, including treatment with presently available agents, as well as with those which may be developed in the future.

References

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