THE pathogenesis of essential hypertension, which accounts for 95 per cent of hypertensions seen clinically, is still unknown despite extensive research during the past 25 years. These studies, however, have indicated that there are neurogenic, electrolyte, endocrine, and renal changes in pathophysiology that may have pathogenetic significance for essential hypertension. These changes may be interpreted to mean either that essential hypertension is a generic classification consisting of several distinct types of hypertension or that it is a single clinical entity with various degrees of functional alteration in different body systems. The former is presently the majority opinion, although only future research can determine which viewpoint is valid.

The pathogenetic relation of malignant hypertension to essential hypertension is also controversial. Although some authorities regard the 2 conditions as qualitatively different, most probably malignant hypertension is usually a greatly accelerated and accentuated form of essential hypertension. The same may be said for arteriolonecrosis, the typical lesion of malignant hypertension, in relation to arteriolosclerosis, the typical lesion of essential hypertension.

Recent reports confirm the role of heredity and body type in essential hypertension, but obviously these factors must operate through pathogenetic and pathophysiologic mechanisms that only future research can elucidate. Aging and obesity are contributory but not basic factors in the development of essential hypertension. The cardiac output, blood volume, viscosity of the blood, and elasticity of the arteries are within normal limits in early essential hypertension. The hypertension is due to increased resistance offered by the systemic arterioles, which in the beginning is due to increased tonus of arteriolar smooth muscle. Basically then, elucidation of the pathogenesis of essential hypertension involves determination of the mechanism responsible for increased tonus of arteriolar smooth muscle.

The neurogenic factor in essential hypertension is considered by its proponents to have origin in nervous tension or corticohypothalamic imbalance, as a consequence of which the vasomotor system is periodically and later continuously set at a higher level of activity with resultant increased tonus of the smooth muscle of the systemic arterioles. The evidence for this concept is circumstantial and includes the antihypertensive effects of tranquilizing, sedative, and vasomotor blocking drugs in some patients and the apparent curative effect of sympathectomy in 5 to 10 per cent of patients. One recent report denies increased vasomotor nerve activity in essential hypertension, and certainly the burden of proof rests on those who maintain that such activity is chronically operative and pathogenetic in essential hypertension.

There have been many attempts to produce persistent hypertension by alteration of the nervous system of animals. Some of these have been successful. Strong auditory stimulation of rats selected for emotional instability leads to hypertension that has not been sufficiently studied to determine its pathophysiology. Section of the buffer regulatory (carotid sinus and aortic depressor) nerves produces a high-level hypertension in dogs and rabbits. While buffer-nerve hypertension differs in important
respects from essential hypertension; viz., increased cardiac output, increased heart rate, chronically increased vasomotor tonus, and absent buffer-nerve reflexes, its further investigation may yet yield information of value for a better understanding of essential hypertension. A persistent, low-level hypertension has been produced in a few dogs by successive ligation in the neck of the arteries supplying the brain. Recently a mild hypertension has been produced in rabbits by ligation of the internal and external carotid arteries. A high-level, persistent hypertension has been produced in dogs by constriction of the branches of the carotid arteries above the carotid sinus. Since the hypertension of these dogs appears to resemble essential hypertension, its further study may be important to our knowledge of essential hypertension.

The possibility that essential hypertension may be due to increased secretion of an as yet unidentified adrenal cortical steroid with a pronounced pressor effect and minimal effects on sodium and carbohydrate mechanisms is suggested by the demonstration of mild alterations in sodium and water metabolisms in essential hypertension. Thus the patient with essential hypertension retains sodium and water more readily than the normotensive person on a sodium-free diet, loses more sodium in the urine under hydropenic conditions, excretes more sodium and water under load, and shows an increased sodium content of the renal arteries and psoas muscles. Moreover, a minority of patients with essential hypertension shows a significant reduction in blood pressure on a low-sodium diet. Whether these changes in sodium metabolism are cause or effect in relation to the pathogenesis of essential hypertension remains to be determined.

There is a recent report of increased aldosterone in the urine in essential hypertension. Also mild adrenal cortical insufficiency resulting from adrenalectomy and minimal substitutive therapy produces an antihypertensive effect in some patients with severe essential and malignant hypertension. A minority of patients with essential hypertension shows increased norepinephrine in the urine and according to a recent report, patients with essential hypertension show increased antidiuretic hormone in the urine. Certainly a more thorough study of the anterior pituitary, adrenal cortex, and other endocrines in essential hypertension is needed, particularly with the improved methods for determining adrenal cortical steroids now available. Presently the burden of proof is on those, including Selye, who maintain that altered anterior pituitary-adrenal cortex function is pathogenetic in essential hypertension.

Large doses of crude anterior pituitary extract, somatotrophic hormone, desoxycorticosterone, aldosterone, or sodium chloride produce hypertension in rats, but less readily or not at all in dogs. Although these experimental hypertensions appear to resemble those of patients with pituitary basophilism or adrenal cortical tumors rather than essential hypertension, their further study may throw light on the pathogenesis of essential hypertension.

From the time of Bright, clinical hypertension was regarded as usually of renal origin, but at the end of the last century the concept rose that essential hypertension is of unknown cause and not due to renal mechanisms. This concept still dominates clinical thinking, although challenged by Goldblatt and other laboratory workers. The absence of commonly measurable changes in renal function in early essential hypertension does not rule out the possibility of more subtle changes in renal physiology that may be pathogenetic. The possibility of such changes is suggested by the presence in essential hypertension of an increased plasma concentration of vasoexcitatory material (VEM) produced by the kidney, an altered tetrazolium histochemical pattern in the kidney, and the ability of the kidney to form VEM aerobically. In contrast to normotension, these findings are also present in experimental renal hypertension that is produced by constriction of the renal arteries in dogs.

Failure to find a difference between the renin concentration of the plasma in normotension and essential hypertension has frequently been cited against a pathogenetic role for renin and the kidney in essential hypertension. However, recently it was shown that hypertension could be maintained by the intravenous infusion of rabbit renin into the rabbit in an amount that
produced an increase in plasma renin concentration not detectable by present methods of assay. Moreover, by means of a technic employing 250 ml. of blood per determination, the hypertensin content of the blood has been reported increased in essential hypertension. This finding suggests that the renin content of the plasma in essential hypertension should be reassayed with the use of larger amounts of blood. Obviously the burden of proof is still on those who believe that the kidney is pathogenetic in essential hypertension. In any event, renal arteriolosclerosis developing during the course of essential hypertension can accentuate and accelerate the course of the hypertension on the basis of Goldblatt’s classic experiment.

Constriction of the renal arteries, a figure-of-eight tie or a cellophane capsule about the kidneys, or injection of a silica solution into the renal arteries produces hypertension in various species of laboratory animals that resembles in many respects essential hypertension. Severe constriction of the renal arteries produces experimental malignant hypertension. Obviously the similarities of these experimental hypertensions to essential and malignant hypertensions in man do not necessarily mean even a partially common pathogenesis. Complete nephrectomy with renal excretory function substituted by peritoneal lavage or the artificial kidney, produces hypertension in dogs and rats, but its relationships to experimental renal hypertension and essential and malignant hypertension are still obscure. Nevertheless, continued study of these experimental hypertensions is important for our understanding of essential hypertension.

Antirenin to hog renin that is actively produced or passively administered is antihypertensive in dogs with experimental renal hypertension, renal (pyelonephritic) hypertension, and spontaneous (essential?) hypertension, suggesting that these hypertensions are on a renal, renin basis. Unfortunately, while antirenin to hog renin neutralizes dog renin, it does not neutralize human renin. A number of attempts to modify the antigenicity of hog renin so that its antirenin will neutralize human renin have been unsuccessful. If a future attempt should succeed, the way would be clear to determine what percentage, if any, of patients with essential hypertension have their hypertension on a renal, renin basis. Antirenin to human renin that is prepared in the dog, which neutralizes only primate renins, is antihypertensive on passive administration to monkeys with hypertension produced by renal artery constriction. We are presently stockpiling antirenin to human renin with a view to a similar experiment in essential hypertension. Although human and monkey renins are similar antigenically, human renin produces an antirenin in the monkey that exerts an antihypertensive effect in experimental renal hypertension in this species. The possibility of the reverse experiment in essential hypertension is hampered by the minute amount of renin in monkey kidneys, but the number of kidneys used per year for poliomyelitis virus culture would be sufficient for a crucial experiment.

Since the pathogenesis of essential hypertension is unknown, treatment must be based on pathophysiology and empiricism. Current treatment affords symptomatic relief and prolongs life in some patients but whether it is capable of altering the basic cardiovascular disease process can only be conjectured. To the degree that present therapy exerts an antihypertensive effect, it should delay the onset and progress of arteriolosclerosis and atherosclerosis.

Obviously much work remains to be done. Neurogenic, endocrine, and renal factors in essential hypertension must be further explored and other avenues investigated. The possibility of a basic pathogenetic change in the contractile proteins, electrolytes, enzyme systems, and other metabolic processes of vascular smooth muscle must be studied. The normality of pulmonary arterial pressure in early essential hypertension has been too readily explained on the basis of the sparse smooth muscle of the pulmonary arterioles. Long-term physiologic, psychologic, sociologic, and epidemiologic studies may yield important information. Barring a fortunate, accidental finding, treatment will be specific, curative, and preventive only when the pathogenesis of essential hypertension is determined.

George E. Wakerlin
REFERENCES


Medical Eponyms

By Robert W. Buck, M.D.

Mönckeberg’s Arteriosclerosis. Dr. J. G. Mönckeberg (1878–1925) first wrote of “Calcification Confined to the Media of the Arteries of the Extremities and its Relation to Arteriosclerosis” (Über die reine Mediaverkalkung der Extremitätenarterien und ihr Verhalten zur Arteriosklerose) in Virchow’s Archiv für pathologische Anatomie und Physiologie und für klinische Medizin 171: 141–167 (January 2), 1903, when he was working in the pathological-anatomical institute of the General Hospital at Hamburg-Eppendorf.

“In conclusion I should like to state:

1. Calcification of the media is much more frequent in the arteries of the extremities than arteriosclerosis.

2. If the arteries of the extremities are palpable as ‘stiff, tortuous, brittle tubes,’ we are dealing in an overwhelming majority of the cases with a calcification of the media, not with arteriosclerosis.

3. It is not possible to decide without other evidence as to the existence of arteriosclerosis of the central vessels, either from the degree or the extent of peripheral calcification of the media. Both diseases are frequently found together, but cases occur of very marked medial calcification of the peripheral arteries without any arteriosclerosis of the internal vessels.”
Editorial: Pathogenesis of Essential Hypertension
GEORGE E. WAKERLIN

Circulation. 1957;15:1-4
doi: 10.1161/01.CIR.15.1.1
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1957 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/15/1/1.citation

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/