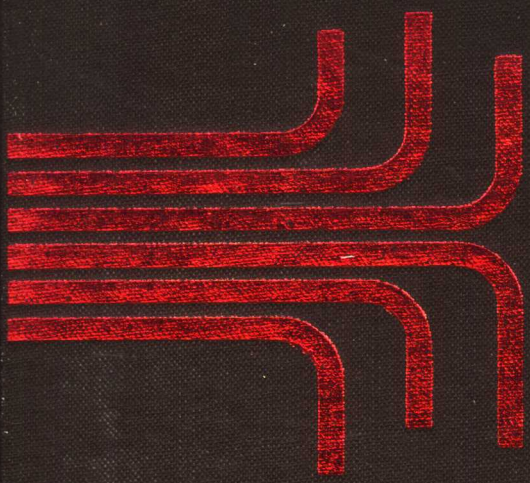

VOLUME 2

CARDIAC AND VASCULAR DISEASES

HADLEY L. CONN, JR.
ORVILLE HORWITZ

CARDIAC
and
VASCULAR DISEASES

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Chapter 32. Systemic Arterial Hypertension

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A disease of insidious onset, hypertension usually is discovered during a routine examination performed for military, insurance, or pre-employment evaluation. The lack of symptoms associated with the onset of hypertension means that many patients may be hypertensive for years before the diagnosis is made. Thus statements as to the incidence of hypertension are necessarily vague. Estimates of the number of hypertensive individuals in the United States range from 15 to 20 million. Both the primary effects of hypertension and its association with the acceleration of atherosclerosis and death due to cardiovascular sequelae has made its early diagnosis and treatment a matter of great importance.

Historical Background.[1] In 1711, the Reverend Stephen Hales inserted a brass pipe into the left crural artery of a mare and, using a straight column of water and a long ruler, demonstrated that flowing blood exerted a pressure on the wall of the vessel. This first measurement of blood pressure was made by one who was not a physician, but who, in his search for truths in nature, made many noteworthy scientific contributions. One hundred seventeen years later, Jean Poiseuille, while a senior medical student, discovered the usefulness of the mercury manometer for measuring blood pressure. He called his instrument an Hémodynamomètre. Bright's classic description of a hard pulse, left ventricular hypertrophy, albuminuria, and pathologic evidence of renal disease was made in 1836. His correlation of these observations was all the more remarkable because it preceded by many years our current concept of hypertensive cardiovascular and renal disease. Ludwig Traube was the first to describe increased arterial tension in man in 1856; his report was based on palpation of the arteries of patients at the bedside. For many years, it was commonly felt that increased arterial tension was always a consequence of pre-existing renal disease or arteriosclerosis. Sanderson, in 1867, was one of the first to suggest that arterial hypertension might exist before clinical signs of kidney disease appeared. In 1874, Mahomed described the prealbuminuric stage of Bright's disease when he found that increased arterial pressure might precede the appearance of symptoms of renal disease. At that time it was thought that hypertension represented an early stage of Bright's disease. It was not until 1879 that Mahomed became aware of the existence of increased blood pressure in the absence of renal disease. In 1895, Sir

Clifford Albutt clearly separated the syndrome of essential hypertension from Bright's disease. It was Albutt who introduced the term "hyperpiesia" in England. The term "essential hypertension," used in America, was derived from the German "essentielle hypertonie," introduced by Frank in 1911.

It was not until 1896 that Riva-Rocci introduced the first clinically acceptable sphygmomanometer, which occluded the upper arm with an inflatable rubber cuff until it obliterated the brachial artery pulse. In 1905, Nikolai Korotkoff[2] introduced the auscultatory method for measuring systolic and diastolic brachial artery pressures. Many subsequent studies have verified the reliability of using the Korotkoff sounds in the indirect measurement of blood pressure. The American Heart Association currently defines the systolic pressure as the first sound heard and the diastolic pressure as the disappearance of sound,[3] although this may be revised to conform with recent investigations.[4-6]

In 1898, the Scandinavians Tigerstedt and Bergman added credence to the thought that all hypertension was of renal origin, by producing an extract of fresh rabbit kidney cortex which had a blood pressure raising effect and which they named renin. Subsequently, many investigators tried in the laboratory to produce a clinical picture resembling essential hypertension by damaging, destroying, or changing the kidneys in some way. In most of these studies, the final result was that of hypertension and uremia. It was not until 1934, when Goldblatt restricted renal arterial pulsatile blood flow by placing a silver metallic clamp on the renal artery of a dog,[7] that a form of hypertension was produced which was similar to essential hypertension. In 1935, Page[8] and Braun-Menendez[9] independently added to our understanding of the hormonal mechanism of renal hypertension by discovery of a potent pressor substance produced as a result of the interaction of renin and a circulating alpha-II globulin produced by the liver. By later agreement they called the substance angiotensin. As a clinical application of this work, the current examination of hypertensive patients now consists in the search for those with renovascular hypertension who may be cured by surgical correction of their disease. The list of important contributing investigators has grown long as the effort to search for specific etiologic factors in hypertension progresses. A major goal of this research will be reached when the term "essential hypertension" need no longer be applied to our patients.

Physiologic and Clinical Characteristics

Definition of Hypertension. Blood pressures consistently greater than 140 mm Hg systolic and/or 90 mm Hg diastolic are considered elevated and abnormal. Longer life is associated with blood pressures considerably below average. With a rise in blood pressure, mortality rate increases correspondingly.

Labile Hypertension versus Fixed Hypertension. The onset of hypertension can only be documented when the patient has submitted to a physical examination. Unlike acute illnesses such as pneumonia, the initial elevation of blood pressure[10] is not announced by specific symptoms. An initial period of blood pressure lability, sometimes called the prehypertensive state,[11] may appear first. Its duration is extremely variable, ranging from several months to more than 25 years.[12,13] During this initial or labile phase, the primary etiologic disturbance seems to be functional in nature since structural pathologic changes are rarely demonstrated. Physical examination performed at that time will fail to disclose any evidence of vascular changes. Furthermore, laboratory evaluation will indicate normal organ function. It is during this phase of hypertension that abnormal tone of the sympathetic nervous system has been suggested to account for the clinical findings.

Most patients exhibit true diastolic pressure elevation representing an increase in peripheral resistance, but some exhibit only systolic elevation. In the latter group peripheral resistance is normal or low and cardiac output is increased[14,15] With persistence of either the increased cardiac output or increased peripheral resistance, the resulting elevation in arterial blood pressure

tends to persist. Now one may demonstrate anatomically hyperplastic intimal sclerosis developing in the renal arterioles with the result that lability of blood pressure is replaced by more persistent or fixed hypertension. Examination discloses vascular disease in the target organs and laboratory evaluation of renal function may offer evidence of early impairment. This phase of the disease is usually of shorter duration than the labile phase and calls for more energetic application of antihypertensive therapy. Finally, in the natural course of hypertension, one encounters the terminal phase of target organ decompensation when symptoms can be related to failure of the function of the target organs involved.[16-18] At this point, treatment of hypertension is usually of little avail. Thus the distinction between labile and fixed hypertension has obvious prognostic and therapeutic implications.

Systolic Hypertension. Probably the most common disease state with which systolic hypertension is encountered is that of arteriosclerosis of the aorta and its main branches. Here antihypertensive therapy, if effective, would be helpful in preventing the blood pressure peaks which are known to occur in this type of labile hypertension.[14] Potent antihypertensive drugs are definitely contraindicated since they are not well tolerated and the effect of precipitous drops in blood pressure may be disastrous. In patients in the older age group, there is a high incidence of systolic hypertension associated with loss of elasticity of the aorta secondary to arteriosclerosis. This type of systolic hypertension is due to increased arterial rigidity and is a different entity from diastolic hypertension, in which arteriolar constriction is paramount. There is no evidence that generalized arteriosclerosis produces diastolic hypertension except when renal artery stenosis is involved. The hemodynamic changes responsible for this type of systolic hypertension relate to the fact that during ventricular systole, the increase in intraluminal pressure per unit of aortic stretch is greater as the elastic arteries become more sclerotic. During diastole, the elastic recoil of the aorta and other large vessels prevents the pressure from falling as low as it would in an absolutely rigid system and thus maintains a flow of blood while the ventricles are filling for another systole. Elasticity of the large vessels enables them to store some of the kinetic energy of ventricular systole in the form of potential energy of elastic tension, which is then reconverted by elastic recoil during diastole into the kinetic energy of flow. If the reservoir of the aorta and central arteries has lost its elastic distensibility, it no longer "stores" as much blood during systole and more must immediately enter into the peripheral arteries. Diminished elasticity of the large arteries tends to lower the diastolic pressure because of the diminished elastic recoil of the aorta and its large branches, which are important in the maintenance of the diastolic blood flow and pressure.

We have already noted another form of systolic hypertension which may occur early in the onset of essential hypertension in those patients who exhibit an increase in cardiac output with a normal or low peripheral resistance.[15] These patients seem to follow a more benign course than those whose hypertension begins with the more usual pattern of normal cardiac output and high peripheral resistance.

Among those with a high cardiac output as a cause of systolic hypertension are patients with severe anemia, thyrotoxicosis, beriberi, and arteriovenous fistula. In anemic heart disease, the cardiac output is usually increased when the hemoglobin falls to 7 Gm per cent or less. The cardiac output in thyrotoxicosis is generally increased in relation to the increased pulse rate, in anemia to the increased stroke output, and in both to the increased velocity of blood flow.

Third-degree A-V heart block and aortic insufficiency also represent forms of systolic hypertension in which the high cardiac output is related to increased stroke volume. Marked slowing of the heart in complete heart block produces increased filling of the left ventricle and an increased cardiac output per beat resulting in a systolic rise in blood pressure. Coarctation of the thoracic aorta has been considered a mechanical cause for systolic hypertension related to reduced capacity of the aorta and an increase in the systolic discharge of the left ventricle.[19] Obviously in such abnormal hemodynamic states, treatment should be directed at the specific cause of the increased cardiac output and should not include the

use of nonspecific antihypertensive drugs.

Diastolic Hypertension. All other forms of hypertension discussed subsequently in this section fit the category of diastolic hypertension in which the fundamental hemodynamic alteration is an increased resistance to the outflow of blood in some portion of the systemic arteriolar bed.[20,21] The diastolic blood pressure is representative of the residual impelling force in the circulation during cardiac diastole. Mechanisms responsible for an increase in peripheral resistance and elevation of diastolic pressure are extremely complex. They involve neurogenic and humoral influences which arise in the body as a result of many diverse disease entities and finally converge on a final common pathway of arteriolar constriction.[22-28]

Essential Versus Malignant Hypertension. The term essential hypertension refers to a state of elevated diastolic blood pressure for which no specific etiologic factor has been disclosed. Unfortunately those patients labeled as having essential hypertension constitute the great majority (80 to 85 per cent) of those with elevated blood pressure, even after extensive clinical studies.

The term malignant hypertension is gradually being replaced by the more descriptive term *accelerated hypertension.*[29-31] This term refers to the rapidly progressive phase of hypertensive vascular disease, which may begin de novo or may represent an alteration in a previously benign hypertensive course. Accelerated hypertension is commonly associated with severe renal insufficiency.[32] The diastolic pressures reach levels of 140 mm Hg or more. Examination of the ocular fundi may disclose papilledema and characteristically discloses hemorrhages, exudates, and advanced vascular narrowing.[33] This syndrome was called malignant hypertension because of its highly fatal course prior to the availability of effective antihypertensive therapy. In 1939, the five-year survival rate was 2 per cent in such patients.[33] At present, however, as a result of improved antihypertensive therapy, approximately 50 per cent may be expected to survive five years.[34-36]

Classification of Hypertensive Vascular Disease. In order to assess intelligently the results of the many therapeutic regimens designed for the management of the hypertensive patient, there has been an obvious need for some classification to indicate not only the severity of the blood pressure elevation, but also the degree of associated vascular impairment in the heart, brain, eyes, and kidneys. One of the earliest and most widely used classifications was that devised by Keith, Wagener, and Barker,[33] who related the severity of the hypertensive disease to the degree of angiopathy disclosed on examination of the optic fundus. There were four gradations in their classification. Grades I and II indicated mild and moderate degrees of narrowing of the retinal arteries. Grade III hypertensive retinopathy was associated with the appearance of hemorrhages and exudates with further decrease in the ratio of the diameter of artery to vein. The most advanced degree of hypertensive retinopathy was Grade IV and was associated with papilledema. Although this classification is still extremely valuable because of the correlation between the degree of retinopathy and progressive elevation of diastolic pressure, it was recognized that one could not adequately evaluate the severity of hypertension on the basis of changes in the optic fundus alone.[37-39] Smithwick devised a numerical rating system to classify hypertensive patients according to the degree of vascular damage to all target organs.[40] In the Smithwick rating system, the Group I patient would demonstrate no more than a Grade I retinopathy with complete absence of evidence for vascular complications in the cardiac, cerebral, or renal areas. In Group II there might be evidence for vascular abnormalities in the cerebral, cardiac, and renal areas, but the degree of retinopathy would remain no more than Grade I. A patient might also be classified as Group II with Grade II, III, or even IV retinopathy if there were no vascular changes in the cerebral, cardiac, or renal areas. Group III classification was reserved for those whose diastolic pressure remained below 140 mm Hg, but whose vascular disease did not include a cerebral vascular accident, frank congestive heart failure, or phenolsulfonphthalein (PSP) excretion less than 15 per cent in 15 minutes. Finally, Group IV consisted of those patients whose resting diastolic pressures were 140 mm Hg or more. If the diastolic pressure was below 140 mm, the asso-

ciation of a cerebral vascular accident with neurologic residual changes or frank congestive heart failure or PSP excretion of less than 15 per cent in 15 minutes would still result in a Group IV classification. Obviously some prognostic significance was attributed to this classification inasmuch as patients in Smithwick Group I had a very good prognosis with or without therapy, and those in Group IV a poor prognosis, often notwithstanding antihypertensive therapy. It appears that the ideal classification of hypertensive vascular disease has not yet been developed. The general adoption of a uniform classification would help tremendously in the evaluation of the effectiveness of antihypertensive therapeutic regimens.

Profile of the Hypertensive Patient. Although a high familial incidence of essential hypertension has long been recognized, an actual genetic defect has not been discovered.[41] The relative roles of heredity and environment have been the subject of considerable study and controversy.[42] More specific knowledge of genes and their chemical structure must be known before genetic factors can be assigned a definite role in hypertension. However, current theories of the etiology of hypertension do propose an interplay between genetic and environmental factors.[43-45] The genetic determinants are thought to serve an important role in predisposing the patient to the influence to biochemical, dietary, social, or psychologic factors that would precipitate hypertension.[46-48] The interaction of environmental stresses upon an individual's psychobiologic heritage might be important in the physiologic control mechanisms for stabilization of an individual's blood pressure.[49-51] Pickering has concluded that arterial pressure is inherited as a graded characteristic-like height, and that this inheritance is the same in degree over the ranges regarded as normal and pathologically high.[52,53] He feels that essential hypertension represents no more than one end of a frequency distribution curve that is of normal shape when plotted on a logarithmic scale. The importance of this concept lies in the fact that life expectancy is inversely related to arterial pressure and that organic arterial disease and high blood pressure are clearly correlated. Weitz has interpreted the role of heredity as signifying that essential hypertension is the manifestation of a gene inherited as a Mendelian dominant. He found a family history of death from heart disease or stroke occurring much more frequently in patients with essential hypertension than in controls, and in several families, the history of hypertension extended to three or more generations. Pickering's point of view is that essential hypertension is a quantitative deviation from the normal, and that it is an age conditioned, graded characteristic in the distribution of arterial pressure. As evidence for this view, Pickering derived a unimodal frequency distribution curve relating blood pressure and age. Those who oppose this view point with equal assurance to a bimodal distribution curve for these entities. Platt studied the blood pressures of brothers and sisters of hypertensive patients, and plotting them logarithmically, found a triple peaked curve of blood pressure levels at 145/85, 170/110, and 220/125 mm Hg.[54-56] He interpreted the first peak as reflecting patients with no genes for hypertension, the second peak as having one gene from a single hypertensive parent, and the third peak coming from patients who have two genes, each coming from a hypertensive parent. He concluded, therefore, that hypertension is a distinct disease and not simply a variant of normotension. McKusick has expressed the idea that the genetic determination of hypertension may be polygenic in nature and not a simple Mendelian dominant or recessive trait.[57,58] Thus, multiple genetic factors may operate each through a different mechanism to influence blood pressure. This polygenic concept represents an approach similar to Page's Mosaic theory of hypertension.[23] He envisions a multifactorial process in which neural and humoral factors involving particularly the autonomic nervous system, the baroreceptors, and the renin-angiotensin system[59] are important mechanisms for the regulation of the blood pressure.

Vascular Reactivity. There is considerable evidence to suggest that patients with essential hypertension demonstrate increased vascular reactivity[60] to many stimuli such as exercise and psychic stress.[61-63] Some of this hyperreactivity has been attributed to hypertrophy of vascular smooth muscle and some to increased sympathetic nervous ac-

tivity.[64-67] Aldosterone and increased salt intake may result in the hyperreactivity of vascular smooth muscle to circulating humoral substances.[62,68] On the other hand, chlorothiazide, which produces salt depletion, tends to decrease vascular reactivity in the hypertensive patient.[69-71] Antihypertensive agents that cause catecholamine depletion, such as guanethidine and methyldopa, tend to increase the constrictor response of vascular smooth muscle to exogenous catecholamines. Vascular reactivity to norepinephrine[69] and angiotensin[72,73] has been found to be increased in essential hypertension, but not in the hypertension secondary to renal parenchymal disease.[74]

The cold pressor test of Hines and Brown has been widely used as a test for hyperreactivity.[75] When the hand has been immersed for 60 seconds in water at 4° centigrade, the patient lying supine in a quiet room, hyperreactivity is reflected by a maximum rise in diastolic pressure by 15 mm Hg and a systolic rise of 20 mm Hg or more. Vascular hyperreactivity observed in such a study may be correlated not only with the exposure to severe cold, but also with the pain and apprehension associated with the test.[76-78]

Ayman and Goldshine utilized the Valsalva test as a measure of hyperreactivity also.[79] After a resting blood pressure had been reached, following quiet expiration, the breath is held for 20 seconds. A hyperreactive state is suggested if the rise in systolic or diastolic pressure is 10 mm Hg or more. This test, of course, does not involve the element of pain present in the cold pressor test. One of the aims of these studies of vascular hyperreactivity has been to select those who may be considered potentially hypertensive from a group of patients with normal blood pressure. Unfortunately, the accuracy of this selective process has not been established.

Psychogenic Factors. The relationship between acute and transient elevations in blood pressure and nervous or emotional stress has long been recognized.[80-82] It is for that reason most physicians prefer to assess the severity of the hypertension by obtaining multiple blood pressure readings before embarking on a long-term therapeutic program. The level of blood pressure may be affected quite differently by various emotions.[83] For example, surprise, fear, and sexual excitement may increase the blood pressure, whereas anger and disgust may produce very little change.[84-86] Blood pressure measurements during sleep have been helpful in obtaining more accurate information concerning basal levels. The blood pressure tends to drop at the onset of sleep as a result of the absence of psychic and emotional stimuli.[87] After 3 or 4 AM, it then starts to rise slowly and steadily. These changes have been more marked in the systolic than in the diastolic pressure. If sleep is restless or disturbed by dreams, both systolic and diastolic pressures tend to rise. These changes occur in both normotensive and hypertensive patients, but the rise in blood pressure is greater in the latter.

The term basal blood pressure was first introduced by Addis in 1922. It was used to refer to blood pressures obtained in patients before they arose from bed in the morning, a time when the effects of physical, emotional, and metabolic activities might be reduced to a physiologic minimum.[88] Although basal blood pressures may be of help in the evaluation of the response to antihypertensive agents, they have less practical or prognostic significance than the casual blood pressures obtained during an office examination in which psychogenic and other stress factors have not been totally eliminated.[89] Alam and Smirk have given the name "supplemental pressure" to the difference between the basal and casual levels. The effectiveness of any antihypertensive regimen should be assessed against its ability to control hypertension when the patient is subjected to all of the natural stresses of living.

The psychiatrists have characterized the personality associated with a hypertensive patient as exhibiting frustrated belligerence. However, attempts at utilizing psychotherapy and psychotherapeutic drugs in the treatment of all but the mildest and most labile forms of hypertension, have generally met with failure.[90-92]

Other Factors Which Influence Hypertension. There appears to be no convincing evidence that occupation, per se, plays a significant role in the etiology of hypertension. Among the executive class where one

might expect stress to play at least an aggravating role or be a precipitating factor, no significant increase in the incidence of hypertension has been demonstrated. It appears that the reaction of the individual to his environment has a greater effect upon his vascular system than the specific physical or intellectual demands of the individual's job. Thus, the executive who has the ability to face major decisions without becoming ruffled may tolerate the vascular effects of stress much better than the street cleaner or elevator operator who becomes frustrated by his endless and inconclusive work.[93]

Many hypertensive patients tend to be extroverted, conscientious and perfectionistic, exhibiting high ideals, a strong devotion to duty, and honesty. They tend never to be completely satisfied with their achievements and are often highly sensitive to criticism. If the etiologic predisposition to hypertension is represented by genetic factors, then the subsequent introduction of specific psychologic conditions may precipitate the physiologic mechanisms necessary for the eventual development of hypertension. For example, the high incidence of hypertension among American Negroes has been related to the fact that the Negro is trained by experience from earliest childhood in the suppression of aggression. The frustrated belligerence emanating from the social and psychologic factors in his environment may have played a major role in his greater propensity to develop hypertension.[86,94,95]

The age at which the onset of hypertension is documented may be an important part of the clinical history leading toward the diagnosis of an underlying etiologic factor. Hypertension of unknown etiology is said to begin less frequently before age 30 and after age 55. Hypertension beginning in the younger age group should lead to a search for coarctation of the aorta and renal parenchymal disease such as acute or chronic glomerulonephritis as well as fibromuscular hyperplasia of the renal artery and adrenal tumors.[96-99] Hypertension beginning in the older age group is more likely to be systolic in type and associated with loss of elasticity of the aorta and its main branches.[100,101] The prognosis for hypertension that appears after age 55 or 60 is considered better than for that with an earlier onset.[102,103]

The incidence of hypertension is said to be increased in the urban as opposed to the rural population and the Western as opposed to the Eastern civilization. These differences suggest an environmental influence upon blood pressure resulting from any combination of psychologic, social, or dietary factors. Unfortunately, most epidemiologic studies[83] have been found deficient in the adequate scientific sampling of the population necessary for a true statistical evaluation. For example, information derived from surveys of hypertensive patients admitted to the hospital is obviously representative of a highly selected group of people, just as the population in a particular physician's office is representative of certain selected socioeconomic factors. Data derived from large numbers of life insurance examinations must be considered highly selective, since a process occurs in which the physically subnormal are rated and those with severe hypertension are completely rejected or never request examination.[104,105]

The influence of climate, weather, and deviation of altitude and atmospheric pressure upon the incidence of hypertension has not been studied in great detail. Many clinicians have long been aware of a seasonal influence on blood pressure levels, noting particulary a slight fall in blood pressure during the summer months. Similar experience has been described among hypertensive patients moving from a cold to a warm climate. Hypertension is said to be less common among persons living at high altitudes.[106] In spite of the fact that hypoxia may result in increased blood volume and viscosity,[107] the accompanying peripheral vasodilatation usually produces lower blood pressures among natives living permanently at high altitudes. The observation has been made that miners living in the high Andes may have low resting blood pressures in spite of very high hematocrits. Studies of the effect of exercise on blood pressure offer the encouraging observation that hypertension may be less frequent and occur at later ages in those who have been more physically active. With improved physical training, a lesser increase in pulse rate and cardiac output is generated by a specific stress, and therefore the blood pressure response to exercise is less.

Both sex and race seem to play a role in the incidence and severity of hypertensive vascular disease. Hypertension appears to be more common in the female than in the male. However, it is better tolerated during the child-bearing years than is hypertension in the male. Following the menopause, the incidence of hypertension in women parallels and may even exceed that in males. There have been a number of studies comparing the incidence of hypertension in American Negroes with that in American Caucasians and the incidence in American Negroes with that in their African counterparts.[94,95] As might be anticipated, the non-urban Negro living in Africa has a much lower incidence of hypertension than do those of their race who live in a western civilization. Again the psychologic stresses of urbanization seem to have a positive association with the prevalence of the disease. Among those Negroes living in the United States, hypertension is not only more frequent but more severe in both sexes as compared to the Caucasians. The low incidence of renal artery stenosis as a cause of hypertension among Negroes is unexplained.

Although many studies have suggested that the Chinese rarely suffer from hypertension, it is apparent that we are still waiting for good epidemiologic studies.[108] As with Negroes, the movement of Chinese to an occidental urban society has generally resulted in development of an incidence of hypertension comparable to that of the Caucasians in the same civilization.[109]

An association between hypertension and acceleration of atherosclerosis[110] has been based on evidence that vascular beds in the heart, brain, eyes, and kidneys, the so-called "target organs" of hypertension, exhibit advanced degrees of atherosclerosis out of proportion to chronologic age.[111,112] Hyperplastic intimal sclerosis of the renal arterioles is a classic example of the anatomic change thought to be secondary to hypertension. The hypothesis that lipids circulating under high pressure are forced into the intima of blood vessels, particularly at points of vascular bifurcation, is a gross oversimplification. Local synthesis of lipids within the blood vessel wall constitutes another source of atherosclerosis. Both are probably under the influence of stress and adrenal and genetic factors. As will be shown in the discussion pertaining to evaluation of the hypertensive patient, the plan of therapy and prognostic evaluation is greatly influenced by whether examination discloses hypertension alone or hypertension already associated with atherosclerotic changes in the target organs.[113]

Salt and Hypertension. Although the subject of much investigation, the exact role that salt plays in either the pathogenesis or maintenance of hypertension still awaits exact definition.[114] The efficacy of diets such as the rice diet, low in salt, in lowering blood pressure has suggested that a high salt intake in the diet might be responsible for producing hypertension. It has been readily apparent, however, that many people consume large quantities of salt and yet do not develop hypertension. There has been suggestive evidence that hypertensive persons have been heavier salt users than have normotensive people.[115] Epidemiologic studies have suggested a higher incidence of hypertension in geographic areas where excessive amounts of salt may be consumed.[116]

The distribution of sodium and its elimination by the kidney are altered in the patient with essential hypertension.[117] The arterial wall is reported to contain an increased amount of sodium and water. This abnormality in turn may elevate the blood pressure either by narrowing the arteriolar lumen or by increasing the reactivity of arteriolar smooth muscle to circulating vasoactive substances. The kidneys of hypertensive patients excrete a salt load more effectively than do those of normotensive patients.[118,119] Whether the renal handling of salt represents an etiologic or permissive role of the kidney in hypertension has still not been decided.[120] In renal hypertension, angiotensin may cause increased salt excretion through a direct tubular effect which is separate from its pressor action. There is no evidence that water excretion occurring in excess of sodium excretion might cause a relative retention of sodium in hypertensive patients. However, some hypertensive patients have a slightly elevated serum sodium concentration with expanded total body sodium content and increased amounts of sodium and water in the arterial wall. It has already been indicated that the arteriolar sodium content plays a role in vascular

reactivity, the vascular smooth muscle being less reactive when sodium depleted and more reactive under states of high sodium content.[121-123]

There appears to be some neurogenic control of the relationship between vascular reactivity and salt. If sympathetic tone is decreased, salt may be ineffective in increasing reactivity unless administered in greater than physiologic amounts. Certainly, the adrenal cortical steroids also play a role in the relationship between salt and hypertension.[70] Desoxycorticosterone may convert the hypotension of Addison's disease to hypertension if a sufficient amount of salt is added to the diet. Friedman suggested that the regulation of blood pressure may depend in part on the sodium transfer system, which governs the rate of entrance and extrusion of sodium, water, and potassium in smooth muscle cells. He found that vasoconstriction is accompanied by a surge of sodium into the cell while potassium is moving out. Converse changes occur in association with vasodilatation.

The studies of Dahl added weight to the hypothesis that sodium is important in the production of hypertension.[124] By selective inbreeding of rats, he was able to produce two populations, one very sensitive and the other highly resistant to the development of hypertension while consuming a high salt intake. These data would suggest that salt intake is important as an environmental precipitating factor only in the individual with a hereditary predisposition to development of hypertension. It also suggests that manipulation of the salt intake might be helpful in delaying the onset of hypertension and also in its treatment.

The widespread use of oral diuretic agents has resulted in renewed interest in the relationship between body sodium and hypertension. It has become apparent that although one may successfully lower blood pressure, either through effective use of saluretic agents or through very strict salt deprivation, these relationships are too complex to infer that salt is playing an etiologic role in hypertension. The introduction of diazoxide,[125] a thiazide derivative that lowers blood pressure dramatically in spite of the concomitant production of salt and water retention, has introduced negative evidence regarding salt retention causing hypertension. This apparent paradox may be resolved when one considers that diazoxide lowers blood pressure through a direct effect on vascular smooth muscle. In this instance, it is apparent that the vasodilating effect of this drug is more important to the hemodynamics of blood pressure control than is the drug-induced sodium retention.

Enzymatic Defects in Hypertension. The hypothesis has been offered that an inherited abnormality in the genes of hypertensive patients might influence the nature of the norepinephrine complex in the storage granules of the postganglionic sympathetic nerve endings. As a corollary, it has also been suggested that there may be a decreased ability to accept previously released norepinephrine back into the storage pool.[73] Thus norepinephrine, acting in concert with the sodium concentration in arteriolar smooth muscle, may cause increased peripheral vasoconstriction. Another search for enzymatic defects in hypertension concerned the possibility that monoamine oxidase or catechol-o-methyl transferase might be present in amounts inadequate to degrade the usual concentrations of catecholamines. The fact that higher than normal levels of catecholamines have not been found in patients with essential hypertension could be interpreted as indicating that alternate metabolic pathways have been substituted. Another suggested possibility is that one or more of the angiotensinase enzymes is not neutralizing the normal production of angiotensin, thus permitting a higher range of blood pressure.

Trace Metals and Hypertension. Schroeder has been the foremost proponent of the idea that trace metal imbalance may contribute to the development of arterial hypertension.[126,127] Deficiency of one of these trace metals in a metallo-enzyme complex, either by depletion or displacement by another more or less active metal, could be expected to produce a metabolic disturbance. Among the metals with possible harmful effects, lead has been considered a possible cause for many chronic diseases including hypertension.[128] In severe lead poisoning, acute hypertensive encephalopathy may be a major problem in therapy. Lead salts act as a vasoconstrictor in the perfused dog leg, causing vascular smooth muscle to contract.