# Achievements in Hypertension: A 25 Year Overview

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**Only 25 years ago, the field of hypertension was challenged by retrospective clinical data and epidemiologic information suggesting that an elevated arterial pressure is a major risk factor for enhanced cardiovascular morbidity and mortality. Not only was antihypertensive therapy looked on by many as dangerous and fraught with severe and undesirable side effects, but its validity in reversing the course of disease was not yet demonstrated. This review discusses the dramatic new information amassed over the past 25 years that points to the new physiologic and clinical concepts concerning hypertension. It considers impressive new diagnostic techniques and methods designed to identify secondary forms of hypertension and target organ involvement. In summary, it outlines the feasibility of reversing overall (and cardiovascular) morbidity and mortality with an array of antihypertensive agents that provide the therapeutic ability to suppress most pathophysiologic pressor mechanisms of hypertensive disease. The lesson is clear: hypertension provides the greatest available challenge to the new era of preventive cardiology in the 21st century.**

An invitation to review the past 25 years of achievement in the area of the hypertensive diseases for the inaugural issue of the *Journal of the American College of Cardiology* is a great honor. Over this past quarter-century, there has been an array of outstanding successes and achievements, many by fellow members of the College. During these years, major important and fundamental concepts were introduced concerning the mechanisms underlying the control of arterial blood pressure and the pathogenesis of hypertensive diseases. Diagnostic techniques were introduced that ushered in the concept of selective angiography and organ scans. These, together with novel methods for measuring vasoactive substances and hormones, have provided new dimensions for assessing body function.

Over these past 25 years, antihypertensive drugs have been synthesized and provide the means to dissect the nephron, the autonomic nervous system and even vascular smooth muscle machinery with chemical precision. These agents have improved in sophistication from the massive "blockbusters" of the ganglionic blocking agents to the chemical "rifle bullets" that target specific intracellular and cellular wall chemical systems with remarkable accuracy. Moreover, these new pharmacologic compounds have provided the way for new cardiovascular therapeutic concepts including the role of sodium and water in volume loading and unloading in heart failure and shock, the reduction of ventricular afterload in heart failure, pharmacologic catecholamine receptor inhibition with its implications in treatment of arrhythmias, the inhibition of the renin-angiotensin system in heart failure and the blockade of adrenergic function in the treatment of ischemic heart disease. The feasibility of multicenter clinical trials was demonstrated and the safety and efficacy of antihypertensive therapy were established, heralding a new era of preventive cardiology and the beginnings of a reversal of the major cause of death in the United States and the western world—cardiovascular disease.

These, indeed, have been years of achievement in the field of hypertension, and the gains have had a major impact not only on the entire discipline of cardiovascular medicine, but on overall biologic knowledge and morbidity and mortality worldwide. This review is not intended to provide an all inclusive review of the major achievements in the hypertension area. Many textbooks (1–4) published in recent years have been oriented to this purpose. It is intended to provide the interested reader with an overview of an exciting and productive area of cardiovascular medicine, the contributions of which continue to be realized by other branches of medicine.

## Epidemiology

It was in the area of hypertensive diseases that many epidemiologic studies with cardiovascular and broader medical implications had major impact over these 25 years. These

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studies have 1) demonstrated the overall prevalence of hypertension in the community (5,6); 2) provided definition of the levels of arterial blood pressure that carry the greatest risk of increased morbidity and mortality (7–9); 3) defined racial groups that seem to be at greater risk (5,10,11); 4) demonstrated interacting factors associated with the elevated arterial pressure that confer this increased risk of cardiovascular morbidity and mortality; and 5) pointed the way to more logical approaches to treating populations and, one hopes, to programs of prevention.

**Definition.** Studies reaching their peak of productivity in the early 1960s pointed to the unimodal and continuous distribution of arterial pressure levels in any population group (12). However, it was the actuarial studies performed by insurance companies that demonstrated, with clear significance, the prognostic implications of pressure that exceeded certain levels (13,14). Although these data demonstrated the prognostic import of the elevated arterial pressure, they, of course, could not imply that reduction of pressure would alter long-term survival of persons with high pressures. This was the challenge for future prospective clinical trials. Nevertheless, they did reveal the necessity for additional work to demonstrate those pressure levels that carry the greatest risk. In the early 1960s, the long-term prognostic Framingham Study (15) was begun, which provided much of the impetus for other studies worldwide that identified the factors that increase cardiovascular morbidity and mortality. The early reports from Framingham demonstrated that the higher the pressure, systolic or diastolic, the greater the cardiovascular risk (7). These studies also defined the risk in subpopulation groups: that in general, men have higher arterial pressures than women (at least until the menopause) (16); that there was a greater prevalence of higher pressures in the black population than in the white, and that at any age there was a greater prevalence of black patients with high pressures than of white patients (17); and that hypertension was the major cause of congestive heart failure in both men and women (18). Data also indicated that the most common form of hypertensive disease, essential hypertension, most likely has its onset in youth and that the blood pressure level tracks with the individual throughout adolescence into adulthood, eventually to surface as clinical hypertension in midlife or earlier (19,20). These studies were complemented, confirmed, enchanced and supported by a large number of studies all over the world, and subsequently supported by prospectively designed studies aimed to demonstrate that a reduction of arterial pressure would reverse this increasing incidence of cardiovascular morbidity and mortality.

**Role of dietary sodium.** Studies conducted experimentally in the laboratory (21) have pointed to the role of the sodium ion in elevated arterial pressure. These studies have been supported only in part by epidemiologic investigations (22). Nevertheless, they indicated that the quantity of dietary sodium ingested by different populations varies tremendously around the world and that there seems to be an important direct relation between the amount of salt ingested in a particular population and the prevalence of hypertension (23,24). However, in those populations that ingest little sodium (about 10 mEq daily), hypertension seems to be nonexistent (25) and, if the dietary sodium content is restricted to less than 70 mEq daily, there seems to be no "normal" increase in systolic or diastolic pressure with aging (26). These studies suggest that the problem of hypertension seems to be greater in so-called westernized, industrialized or "acculturated" societies (27). The role of sodium in the pathogenesis of hypertension continues to be under intensive epidemiologic, clinical and experimental investigation; moreover, its specific mechanism in elevating arterial pressure requires additional study. It is, therefore, premature to conclude that dietary sodium restriction will prevent the development of hypertension; however, dietary sodium restriction is recommended for patients with hypertension as an important therapeutic adjunct (28).

**Other associations.** Epidemiologic studies also have demonstrated a more than chance association between other diseases and hypertension. There is a greater prevalence of hypertension in patients with altered carbohydrate metabolism and diabetes mellitus (29–32). And, conversely, there is a greater prevalence of diabetes mellitus and carbohydrate intolerance in patients with hypertension than in the general population (31,32). The precise mechanism explaining this association has not yet been offered, and one study has even challenged this long-held assumption (33).

*Other reports (34,35) have shown a greater prevalence of elevated uric acid levels in patients with hypertension than in the general population.* The reason for this association also remains unexplained, but a recent study (36) suggested that the elevated serum uric acid may reflect early hypertensive vascular disease changes in the renal circulation rather than altered purine metabolism; however, both alterations could provide the explanation. A third metabolic abnormality—elevated levels of lipids and lipoproteins (5,7,9,37)—has been found in patients with hypertension.

*Among other alterations that characterize the "profile" of a population of hypertensive patients are increased body mass and a faster heart rate.* With respect to the overweight characteristic, there is a greater prevalence of hypertension in a population of obese persons (38,39), and patients with hypertension seem to weigh more than comparable normotensive persons (40,41). The faster heart rate in patients with each form of hypertension (42) is an intriguing physiologic finding because one would expect heart rate to be slower as arterial pressure increases. Whether this is a reflection of the "reset baroreceptor mechanism" in experimental hypertension (43) or whether it represents a pathogenetic mechanism that initiates the hypertensive process must also be resolved. Each of the areas cited has been

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suggested through epidemiologic investigations and each is under intensive clinical and experimental study. Finally, these and other factors (including cigarette smoking, personality type and alterations of other dietary ionic constituents, certain foods, chemicals and drugs) have been shown not only to participate in the hypertensive process but also to be associated with increasing morbidity and mortality from other cardiovascular diseases (44,45).

## Pathophysiology

Over these past 25 years, there have been tremendous gains in knowledge of the regulation of arterial pressure. This new information has contributed much to our understanding of the pathophysiology of hypertensive diseases and other cardiovascular illnesses. Currently, most workers in this area conceive of essential hypertension as a multifactorial disease that is brought about by certain inborn hereditary, genetic predisposing mechanisms that could interact with the myriad of pathogenetic pressor and depressor physiologic factors (46,47). Some reports (48,49) indicate that identifiable clinical causes or types of secondary hypertension (for example, aortic coarctation, renal artery disease, adrenal adenomas, renal parenchymal disease) represent a very small proportion of the overall population of hypertensive patients. However, with the overall prevalence of hypertension (60 million Americans) reported in the most recent population studies (50), even a 3 to 5% proportion represents upward of 3 million persons (far more than the total number of patients with muscular dystrophy, multiple sclerosis, subaortic stenosis or hemophilia, and possibly as many patients as having homozygous sickle cell anemia). And, most important, some of these persons have remediable forms of hypertension.

An important benefit derived from studies of patients with secondary forms of hypertension has been an improved understanding of the mechanisms that control and maintain arterial pressure (Table 1). It therefore follows that ability to assess participation of certain physiologic mechanisms may lead to improved means to establish diagnosis and to introduce more specific therapy.

**Circulatory autoregulation.** In recent years, several pathogenetic concepts have been advanced concerning the hemodynamic and other mechanisms underlying the pathogenesis and elaboration of hypertension. Notable among these were the concepts suggested by Borst (51), Ledingham (52) and Guyton (53) and their co-workers that intrinsic in the pathogenesis of essential hypertensive disease is an altered handling of circulating volume that transiently expands the circulation, increases the cardiac output and arterial pressure and permits a circulatory adaptation (that is, autoregulation) which eventually results in a state of maintained higher pressure that is then associated with an increased total peripheral resistance and normal cardiac output (54). These concepts have received considerable support through experimental studies, although expanded intravascular volume in essential hypertension has not been documented, particularly early in essential hypertensive disease; in fact, the contrary was observed (55,56). Indeed, clinical studies have demonstrated increased cardiac output in the early stages of hypertension (55,57), as well as in more severe disease (58). Nevertheless, it is possible that a circulatory autoregulatory process may occur without an expanded intravascular volume and increased cardiac output. This could be achieved if a normal (or even contracted) intravascular volume is associated with a normal cardiac output that is maintained through increased peripheral venomotor tone and mean circulatory filling pressure that increase venous return to the heart (59). In fact, hypertension developed experimentally in the presence of a reduced or normal intravascular volume and cardiac output when the animals were pretreated with beta-adrenergic receptor blocking drugs (60) or when dietary sodium was restricted (61,62). Thus, the *net* hemodynamic effect is the same as if a normal venomotor tone were associated with an expanded intravascular volume: an increased mean circulatory filling pressure and reduced vascular (postcapillary) compliance (63,64). These same findings of increased arteriolar and venular vascular tone have been shown in a variety of clinical (essential, renovascular) (65) and experimental (spontaneously hypertensive rats and Goldblatt hypertensive rats) situations (63,64).

**Adrenergic factors.** An alternative pathogenetic explanation might be that the increased venomotor and arteriolar tone may be produced by adrenergic stimulation (48,57,66). This mechanism is also compatible with the findings of a faster heart rate, increased cardiac output and increased myocardial contractility early in the developmental stages of hypertension (57,67) and even later in the disease (58). Just how this increased adrenergic input to the cardiovascular system develops remains to be demonstrated; it might be related to supersensitivity of neurohumoral agents (norepinephrine, for example) to the sodium ion (68), to certain defects in catecholamine metabolism or release (69) or even to central stimulation of adrenergic output from the brain by angiotensin (70).

*Other work has shown that plasma catecholamine levels increase as arterial pressure rises in patients with essential hypertension (71),* but this relation may be affected by age, race, sodium and water balance, as well as by other factors

**Table 1.** Mechanisms That Control Arterial Pressure

| | |
|---|---|
| 1. Autoregulatory and hemodynamic | 6. Hormonal mechanisms |
| 2. Mechanical factors | 7. Volume mechanisms |
| 3. Neural mechanisms | 8. Sodium interrelations |
| 4. Catecholamines | 9. Depressor mechanisms |
| 5. Renopressor system | |

(72). Further, in some patients with mild essential hypertension there may be an increased responsiveness of vessels (73) and heart (74) to adrenergic agonists, as well as increased plasma levels of catecholamines (75,76) and cyclic adenosine monophosphate (77). With development of radioenzymatic methods for the measurement of plasma catecholamine levels in small samples of blood, the role of adrenergic participation in essential hypertension should be further clarified (78).

**Renin-angiotensin system.** The latter hypothesis opens discussion of the very active area of clinical and experimental investigation over these past two and one-half decades: the role of the renin-angiotensin system in the pathogenesis of hypertension. These studies have demonstrated the feasibility of measurement of each of the components of this biochemical system (79–82). Until this was feasible, evidence of the relation of this mechanism to the pathogenesis of renovascular hypertension was only circumstantial. Now it is well known that in patients with renovascular hypertension, there are significant increases in plasma renin activity in the venous blood from the affected kidney (83–85). Moreover, pharmacologic interventions are available that can inhibit the release of renin from the kidney (86–88), arrest the biogenesis of angiotensin II (89–91) or interfere with the vascular response to angiotensin II stimulation (92,93) and control arterial pressure under a variety of situations that may inhibit the renopressor system. It is still not known why these therapeutic agents also reduce arterial pressure in patients with normal renin or low renin essential hypertension (94,95).

*Studies have been concerned with characterizing the role of the renopressor system in the pathogenesis of essential hypertension* through the elucidation of the magnitude of plasma renin activity in these patients with respect to appropriate sodium loading and aldosterone secretory and excretory responses (96,97). These studies suggested that perhaps patients with high plasma renin activity have certain prognostic characteristics (more severe course of disease, more complications, for example) and certain therapeutic prognostic indexes (98), whereas low plasma renin activity suggests other prognostic and therapeutic factors. Although the practical therapeutic lesson is that reduction of arterial pressure through suppression of whatever physiologic pressor mechanism seems to be participating is of paramount importance, it does make clinical sense that the most specific form of therapy with the fewest side effects would be the most logical means to achieve that pressure control. To this end, studies have shown that adrenergic- or angiotensin-inhibiting therapy may be of greatest value in patients with increased plasma renin activity (99,100) or evidence of greater adrenergic input (hyperdynamic circulation) (101), and that patients with the lowest plasma renin activity may be more volume-dependent or will respond better to volume-contraction therapy (102).

*Also known is the great interdependence of physiologic mechanisms*; it is possible that in those patients with higher levels of plasma renin activity who most likely have greater participation of the renopressor system, there is a normal stimulation of certain brainstem centers that provide adrenergic input to the cardiovascular system (70). This, in turn, would provide further stimulation of the renal juxtaglomerular apparatus to release more renin, thereby maintaining the cycle of disease. Thus, it is possible that hypertension (essential hypertension as well as renovascular) may be initiated through an increased release of renin from the kidney or that it might be maintained through participation of this system.

**Aldosterone.** Early in this period under discussion were the exciting reports of Conn (103) and others (104,105) that the very potent mineralocorticoid aldosterone was etiologically responsible for one form of secondary hypertension. In patients with this condition, the hypertension was reversed with surgical removal of the adrenal adenoma; however, subsequent reports indicated that in some patients with primary hyperaldosteronism, hypertension is not reversible. These patients seem to have bilateral adrenal hyperplasia (of the zona glomerulosa) with hyperaldosteronism (106,107) or, additionally, essential hypertension.

*Another area of clinical controversy was related to the observation of normokalemic primary aldosteronism* and the possibility that with this additional compounding problem hypertension may be far more prevalent than previously considered (108). This concern was particularly pertinent in view of the relatively contemporaneous observation of a significant number of patients with essential hypertension having low or suppressed levels of plasma renin activity (96,97). However, this anticipation of upward of 20% of patients with essential hypertension having normokalemic hyperaldosteronism was not borne out and, at present, there is no tangible explanation for the state of low renin essential hypertension.

*As indicated, a significant number of patients with essential hypertension* have low plasma renin activity and, in at least some cases, the condition is volume-dependent (109,110). It has been asked why, in the presence of reduced participation of the renopressor system, there is a normal adrenal cortical response and a normal plasma aldosterone level or aldosterone excretion. To answer this question, some investigators suggested altered responsiveness of the adrenal cortical cell to angiotensin II stimulation (111), and others suggested an additional, as yet unknown, adrenal cortical hormone (112). Evidence in favor of the latter possibility was offered by the occasional findings of newer adrenal steroid substances having weaker sodium-retaining ability (113), and by the normalization of arterial pressure in patients with this condition by treatment with certain agents that arrest all biogenic steroidogenesis pharmacologically (114). In any event, clinical and experimental inves-

tigations in this area of the renin-angiotensin-aldosterone system have been among the most intense in the field of hypertension over the past 25 years (and clearly among the most productive).

**Other mechanisms.** *Vasopressin.* It is clear that other mechanisms participate in the control of arterial pressure (Table 1). Although several have been known for some time to participate physiologically in bodily homeostasis, until recent years their effect in hypertensive diseases had not been studied. Thus, we have known that vasopressin has important implications in the homeostasis of total body water and also has the ability to produce arteriolar constriction. Recent studies have shown that vasopressin may be increased in certain forms of experimental hypertension (115), but this has not yet been shown in human beings (116). Now that methods are available for measurement of this substance, further information will no doubt be forthcoming.

*Prostaglandin system.* Much has been reported concerning the biochemistry and biosynthesis of the many naturally occurring prostaglandin substances (117,118). Some of these compounds are vasoactive and may produce vasoconstriction or vasodilation (119,120), but at present there is insufficient information to incriminate any one of these agents in the pathogenesis of hypertension. We do know, however, that the prostaglandin system interrelates importantly with the renopressor system (121) and that this relation may be demonstrated in the different hypertensive conditions and in the normotensive pathophysiologic state of Bartter's syndrome (122).

*Kallikrein-kinin system.* Not only is the renopressor system interrelated with the prostaglandin and adrenergic nervous systems, but there is also an interrelation with the kallikrein-kinin system (123). Indeed, these two systems share the same enzyme system that activates and inactivates their pressure-mediating agents: the converting enzyme that cleaves the terminal two amino acids from the inactive decapeptide angiotensin I to form the potent octapeptide vasoconstrictor and aldosterone-stimulating agent angiotensin II which inactivates circulating bradykinin, the potent vasodepressor agent (124). Other actions of the prostaglandin and kallikrein systems as they might relate to the control of arterial pressure are their roles in sodium balance (125) and in clotting (126).

*Depressor role of kidney.* Over these past several decades, studies have described a depressor role of the kidney. Indeed, participation of the kidney in maintaining volume homeostasis has been shown to be defective in renoprival forms of hypertension. This is best manifested clinically by the anephric patient whose arterial pressure levels can be controlled by the state of filtration pressure during hemodialysis and by the sodium balance of the patient (127). In addition, a remarkable series of studies by Muirhead and his colleagues (128) has implicated the presence of a renal medullary nonprostaglandin lipid substance that acts as a depressor agent. Investigation progresses in this area, which may also have important clinical implications for the future.

**Sodium.** As indicated, the sodium ion seems to have a major role in the pathogenesis of hypertension (129). This finding received greatest impetus from: 1) epidemiologic studies pointing to the greatest prevalence of hypertension in populations that have the greatest dietary sodium intake (21–27); 2) experimental studies that indicated aggravation of certain types of hypertension with increasing sodium intake (130–133); and 3) clinical studies that showed the increasing arterial pressure with a large sodium intake in patients with borderline hypertension (134) and the better control of arterial pressure in patients treated with sodium-depleted diets (135).

*There has been a series of studies that seems to point to an abnormality in sodium transport across the cellular membrane in patients with essential hypertension* (135–138). Studies recently demonstrated this defect in the sodium-potassium-adenosine triphosphatase system of red blood cells of patients with essential hypertension (but not in patients with renal artery disease) (139,140), suggesting that a genetic mechanism might be related to the pathogenesis of essential hypertension. The same defect has also been found in genetically (spontaneously) hypertensive rats, suggesting an inherited enzymatic regulation of intracellular sodium and potassium exchange (141).

*Natriuretic hormone.* In this regard, it is appropriate to raise the concept of the still to be defined "third factor" or natriuretic hormone that may participate in the pathogenesis of hypertension (142,143). This substance has been suggested to be produced in extrarenal areas in the brain (144) and possibly in the left atrium (145,146). This substance might operate inappropriately in hypertension, producing an altered sodium balance in the hypertensive patient through its renal excretory mechanism and setting in motion some of the mechanisms discussed earlier. An alternative hypothesis has been suggested in which an alteration in the sodium-potassium-adenosine triphosphatase exchange mechanism results in an increased vascular resistance and arterial pressure (147). In this context, the exchange defect results in increased intracellular movement of calcium ions that serves to increase the smooth muscle tone and hence arteriolar resistance (148).

**Obesity.** As indicated earlier, other factors recognized clinically also seem to participate in the elevation of arterial pressure. Studies over the past 25 years (38–41) have pointed to an important role of body mass. Initially, workers suggested that perhaps the greater arm girth of obese persons produced factitious and abnormally high arterial pressure readings. Although this has some effect, it does not entirely account for the association between obesity and high blood pressure. Others have suggested that the excessive food intake associated with the maintenance of the obese state is related to sodium excess and this, too, most likely has some

effect. However, more recent prospective clinical studies have shown that body mass, itself, no doubt also plays an important role (149,150). In these latter studies, patients demonstrated a reduction in arterial pressure on calorie-restricted diets that were augmented by sodium intake to predietary treatment levels (149); this reduced pressure was related to an increased circulating volume and cardiac output (150,151). Just how increased body mass, but not necessarily fatty tissue, elevates arterial pressure is not known. Altered adrenergic participation (152) and participation of the sodium-potassium-adenosine triphosphatase system (153) have been suggested. This is yet another area that will deserve investigative attention over the next several years.

## Diagnosis

As with so many other areas of cardiovascular medicine, the management of hypertensive diseases has benefited greatly over the past 25 years from newer diagnostic techniques. Obviously, without the careful and frequent measurement of arterial pressure using the most ubiquitous noninvasive cardiovascular instrument, the sphygmomanometer, no diagnosis would be possible. Thus, it will always be imperative for all physicians to measure, record and compare with previous measurements the blood pressure of all patients seen in the office.

**Selective catheterization and arteriography.** One of the most important diagnostic methods developed during the 1960s was that of selective arteriography. This technique permits careful radiographic diagnosis of renal artery diseases and the identification of patients with renovascular hypertension. With extensive experience, a radiographic classification of renal artery lesions was developed that suggested not only the pathogenesis of the disease but its natural history (154,155). Patients with atherosclerotic renal artery lesions may or may not have causally associated hypertension, but it is more likely that in patients with nonatherosclerotic lesions of renal arteries, the hypertension is causally related to the renal artery lesion through participation of the renopressor system (156,157). Moreover, these studies permitted some prognosis of the complications of the lesions. For example, patients with the so-called string of beads lesion of medial fibroplasia more than likely had a slowly progressing disease that was not infrequently bilateral. In contrast, other fibrosing lesions may be associated with a greater frequency of obstruction from thrombosis, dissection and aneurysm formation.

The technique of selective angiography soon permitted renal vein renin sampling for determining plasma renin activity and preoperative prediction of surgical correctability of the vascular lesion (83–85). These radiologic techniques also permitted the use of selective adrenal venography and blood sampling for hormone levels (158).

**Measurement of humoral factors.** Diagnosis of various forms of hypertension has been remarkably enhanced with the development of radioimmunoassay techniques (159). This methodology has permitted more physiologic sampling and accurate measurements requiring only small amounts of blood for the determination of plasma levels of plasma renin activity, angiotensin II (still restricted to only a few research laboratories), angiotensin-converting enzyme, vasopressin, aldosterone and other adrenal steroidal hormones and many other substances. In addition, radioenzymatic techniques have permitted measurement of plasma levels of the different circulating catecholamines (78). In regard to these methods, it is important to reiterate the frequently stated clinical warning that any or all medications that patients take (including oral contraceptives) may affect these measurements. Other factors may also alter the accuracy of these measurements, including the time of day when the blood is sampled, whether or not the patient is fasting, whether the patient is in the supine or upright posture, whether the patient has recently smoked a cigarette and the time in the menstrual cycle. Particularly for the cardiovascular physician who collects blood samples by catheterization, care must be exercised in the choice of anticoagulant agent for the sample and whether the sample tube must be placed immediately in an ice bucket and then promptly centrifuged in a cold environment.

**Newer radiographic techniques.** In recent years, the development of digital subtraction angiography has permitted arteriographic visualization of the renal and other arteries, permitting outpatient diagnosis of renal (as well as carotid and peripheral) artery lesions using intravenous injection of contrast material (160). Although this technique is still new and the equipment is not yet in widespread use, its value in defining arterial lesions in patients with hypertension is great, particularly in this era of awareness of cost effectiveness for diagnostic procedures without costly hospitalizations.

**Computed axial tomography.** Another recently developed technique, computed axial tomography (CAT scanning), is particularly useful as a key means of diagnosis of adrenal tumors (especially pheochromocytoma) (161). As an outpatient technique, it is compatible with efforts to attain improved cost effectiveness. Its diagnostic effectiveness can be enhanced with the measurement of plasma catecholamine levels. This technique is also useful for recognition of other types of adrenal tumors, although the diagnostic value is less great because some of these tumors may be extremely minute.

**Echocardiography in left ventricular hypertrophy.** Echocardiographic techniques have become a major diagnostic aid in cardiology, and in recent years have provided accuracy in defining left ventricular hypertrophy in hypertension (162). Thus, although establishment of the presence of left ventricular hypertrophy is a rather simple procedure once it is obvious by electrocardiographic and roentgenographic criteria (163), these are less precise in the earlier stages (162,164,165). Electrocardiographic criteria are more

sensitive than X-ray measurements (163), but echocardiography is still more sensitive with respect to early involvement (162,164,165). In addition, echocardiography is particularly useful in patients with persistently high office blood pressure readings, whose electrocardiogram and chest X-ray films fail to show evidence of ventricular enlargement, thereby suggesting a lack of persistently elevated pressures. Thus, when echocardiographic measurements fail to demonstrate increased ventricular wall thickness or mass, it is unlikely that the office pressure readings remain persistently elevated over a 24 hour period.

Moreover, studies in animals with experimental hypertension (166–170) and more recent studies in patients (171,172) suggest that certain antihypertensive agents will produce regression of left ventricular hypertrophy. Indeed, agents that produce such regression may have less impressive hemodynamic effects (for example, methyldopa, beta-adrenergic blocking agents) than more potent or seemingly more beneficial antihypertensive agents (hydralazine and minoxidil, for example) that fail to cause regression of (or that even aggravate) left ventricular hypertrophy (169). While these findings are intriguing, they are confusing in the light of existing knowledge, and they definitely require more careful experimental and clinical investigation. This might be particularly important when the abrupt rise of arterial pressure that occurs with discontinuance of antihypertensive medication (173) is considered, particularly since there are no data available concerning the performance ability and function of the left ventricle with regressed hypertrophy after the arterial pressure has risen. At this time, experimental studies indicate that left ventricular pumping ability is normal after regression of left ventricular hypertrophy (168,170); however, the ventricle has a greater percentage of collagen after regression than before regression (174), and the pumping ability studies have been reported only for function at normal levels of arterial pressure.

## Clinical Therapeutic Trials

Perhaps no area of clinical investigation has yielded more outstanding dividends in demonstrating efficacy of reduced overall morbidity and mortality than the prospective multicenter clinical trials of antihypertensive agents. Although extremely costly, these studies first demonstrated the efficacy and safety of the wide variety of antihypertensive agents. The contributions of the many pharmaceutical houses in this area are obvious, for it has been through this means of multicenter studies that larger numbers of patients have been subjected to larger scale screening and treatment programs that eventually permit the widespread use of effective antihypertensive agents. These studies have been designed to obtain approval by governmental regulatory bodies for commercial availability.

**Early multicenter trials.** Lessons learned from this approach were applied by pioneering clinical investigators in small scale clinical trials that demonstrated the efficacy of the early antihypertensive agents in reducing arterial pressure and cardiovascular morbidity and mortality (175–178). Soon multicenter studies designed by clinical investigators independent of commercial constraints were instituted; the most notable of these were the now classic trials of the U.S. Veterans Administration under the careful chairmanship of Freis (179,180). These studies initially demonstrated the efficacy of the potent ganglionic blocking agents in patients with severe hypertension and the synergistic value of the thiazide diuretic agents with reserpine or with additional hydralazine. Once the feasibility of the multicenter study involving investigators of wide geographic spread but with central administrative and statistical support was established, a series of studies was undertaken to demonstrate the validity of antihypertensive therapy in reducing morbidity and mortality. Using the same combination of antihypertensive agents shown early to be safe and efficacious (with an appropriate randomly selected, placebo-treated control group), the Veterans Administration Cooperative Study Group first demonstrated the validity of therapy in patients whose diastolic pressure exceeded 114 mm Hg at the onset of the study (181). Next, value of therapy was demonstrated in patients whose diastolic pressures exceeded 104 mm Hg (182); there were too few patients whose pretreatment diastolic pressures were within the 90 to 105 mm Hg range.

**Later trials.** As a result, a number of subsequent studies were designed to attack the problem of so-called mild hypertension. The first reports came from the Hypertension Detection and Follow-up Program (183,184). This 14-center study involved approximately 11,000 patients screened from an overall population of more than 180,000 persons allocated into two treatment groups. One group received standard medical treatment prescribed by community physicians (referred care group) and this therapy included all available health care and antihypertensive agents. The other group received a programmed stepped-care treatment program followed by algorithm by a health care team that was challenged to provide as intensive a therapy as possible using whatever available techniques could be mustered to maintain blood pressure control. These techniques included establishment of pretreatment pressure goals, provision of free medication, transportation to clinics (if necessary), professional follow-up of missed appointments and so forth. Within 5 years, the program demonstrated lower overall and cardiovascular morbidity and mortality rates in patients with all levels of blood pressure elevation including those with mild blood pressure elevation (90 to 104 mm Hg).

These reports were soon supported by studies from Australia and Norway (using placebo-treated, randomly selected patients) which demonstrated similar improvement in morbidity and mortality in patients with mild hypertension (185, 186). Not only was the value of those antihypertensive agents used in the Veterans Administration trials demonstrated, but

also included were other diuretic agents, the beta-adrenergic receptor blocking drugs and adrenolytic agents.

*At the time of this writing, several other multicenter investigations are in progress (187).* One study is designed to learn the value, if any, in improving overall morbidity and mortality by reduction of other cardiovascular risk factors such as obesity, cigarette consumption, hyperlipidemia and control of diabetes (the so-called MRFIT Trial). Others (organized by treatment centers in Western Europe) are designed to learn whether there is benefit from treating hypertension in the elderly patient and some (organized by the U.S. National Institutes of Health) are investigating isolated systolic hypertension.

**Effect of blood pressure control.** This report is not intended to provide a comprehensive overview of all clinical trials involving the use of antihypertensive agents, but in my estimation the prospective therapeutic intervention trials mentioned have provided the outstanding landmarks for our present "state of the art" and improved cardiovascular health derived from an enlightened approach to the treatment of hypertension. Indeed, at the beginning of the 1970s it was estimated that only about one of eight patients with hypertension was receiving effective antihypertensive therapy. The number of patients under treatment has since been vastly increased (188). As a result, it seems fair to say that blood pressure control has, at least in part, accounted for a reduction in the U.S. national cardiovascular mortality from 54 to 50% of all deaths and a 33% reduction in the number of strokes (188). Clearly, this is one of the major challenges for an enlightened era of preventive cardiology as we near the 21st century.

## Therapeutic Agents

One cannot review the accomplishments in the area of hypertension over the past 25 years and neglect the fact that during this period, a remarkable array of agents has been developed. Not only have they had an impact on the treatment of hypertension but clinical investigators and the pharmaceutical industry, working as a therapeutic team, have provided major innovations with these drugs for the treatment of: 1) heart failure (through diurectic agents, vasodilators and converting enzyme inhibitors); 2) angina pectoris (through diuretic agents, the concept of blood pressure reduction, beta-adrenergic receptors and calcium channel inhibitors; 3) cardiac arrhythmias (through concepts introduced concerning hypokalemia, the beta-adrenergic receptor blocking agents and sympatholytic agents); and 4) other cardiovascular problems. Therefore, what might be appropriate in this report of the highlights of this "golden era of hypertension" is a review of the development of this productive area, pointing toward new anticipated areas of therapeutics.

Already available for the practicing physician 25 years ago was the concept that there was nothing "essential" to the clinical problem of hypertension. Contrary to the earlier held concept that "essentielle hypertonie" was necessary to perfuse the vital organs, the therapeutic pioneers clearly demonstrated the value of arterial pressure reduction in patients with severe hypertensive states using the rice-fruit diet (189), ganglionic blocking agents (190), sympathectomy (191) and the veratrum alkaloids (192) and reserpine (193). Pyrogen therapy and renal extracts (194) had already been discarded in favor of these new approaches.

**Diuretics.** *Thiazides.* The modern antihypertensive therapeutic era was born with the introduction of a new effective and potent long-acting agent by Novello and Sprague (195) that produced impressive natriuresis and diuresis associated with an impressive reduction of arterial pressure (196,197). Introduction of this agent, chlorothiazide, was soon followed by the synthesis of a vast array of related halogenated congeners of the thiazide group. Although they differ from each other by chemical structure and certain other characteristics, their physiologic similarities are great. All first produce a natriuresis and contracted plasma (and extracellular fluid) volume associated with a reduced cardiac output, followed by a reduction in pressure and decreased total peripheral resistance (198,199) associated with a vascular attenuation of pressor stimuli and potentiation of depressor stimuli (200). The thiazides are associated with a relatively narrow dose-response curve. Each agent is expected to produce some degree of decrease in glomerular filtration rate associated with natriuresis, kaliuresis, hypokalemic alkalosis, secondary hyperaldosteronism and variable rises in plasma uric acid and glucose levels (201).

*Other agents.* The so-called loop-acting agents (ethacrynic acid and furosemide) acting at the ascending thick limb of the loop of Henle, have a much broader dose-response relation and are of value in patients with impaired renal function (202). Other agents have been synthesized to provide an active means to retain potassium in response to the kaliopenic effects of the thiazide congeners and the loop-acting diuretic agents. Spironolactone achieves this through an active inhibition of aldosterone's action at the distal tubule (203), whereas the other two agents in use today preserve potassium through an amiloride-like effect at the distal tubule that inhibits the sodium for potassium exchange mechanisms (204). Of the two latter agents currently available, triamterene and amiloride, the latter is the more potent in reducing pressure (205).

**Adrenergic inhibiting agents.** Shortly after the introduction of the thiazide diuretic agents, a remarkable new group of drugs was synthesized. These provided more specific inhibition of the sympathetic nervous system than the ganglionic sympathetic inhibition in patients with severe hypertension without producing such central nervous system effects as mental depression (206,207). It was now possible to achieve blood pressure control without necessarily in-

ducing impotence or paralytic ileus. Problems of postural hypotension and reduced organ perfusion to brain, heart and kidney were soon obviated by the introduction of methyldopa (208).

*Methyldopa and clonidine.* At this point, it is appropriate to cite the information added to our concept of adrenergic receptors introduced by Alquist (209) in 1948. Alpha-adrenergic receptors, when stimulated by the neurohumoral substance norepinephine, produced vasodilation, whereas beta-receptor stimulation produced vasodilation and an increase in heart rate and myocardial contractility and metabolism (210). Soon beta-receptors were subclassified as $beta_1$-receptors in the heart and kidney, and $beta_2$-receptors in vessels, bronchi, the gastrointestinal tract and elsewhere. $Alpha_1$-receptors usually were found on vascular smooth muscle cellular membranes at postsynaptic loci mediating vasoconstriction, but they may also be found at presynaptic loci. When $alpha_2$-receptors are stimulated, they inhibit the release of catecholamines from the adrenergic nerve ending as do certain centrally acting postsynaptic receptor stimulating agents (211–213). As a result of the newer information, we are now provided with our current understanding of the action of the central adrenergic inhibitors. Clonidine stimulates central alpha-receptors at the nucleus tractus solitarius, whereas methyldopa must first be metabolized in the neurons of this nucleus to alpha-methylnorepinephrine, which in turn provides the alpha stimulation that inhibits cardiovascular outflow from the hindbrain (212–214). Several additional centrally acting adrenergic inhibitors are under study, but for the purpose of this review they offer no major conceptual addition to the overall understanding of the central mechanisms of the antihypertensive therapeutic agents.

*Phentolamine, phenoxybenzamine, prazosin and urapidil.* Early in the history of adrenergic inhibitors was the synthesis of two compounds, phentolamine and phenoxybenzamine, agents that we now know to inhibit both pre- and postsynaptic alpha-receptors (215). These agents lower arterial pressure associated with reflexive stimulation of the heart. However, the postsynaptic $alpha_1$-receptor blocking compound prazosin produces hypotension without reflexive tachycardia, suggesting an additional action to that of peripheral $alpha_1$-receptor inhibition (216). A new and intriguing agent, urapidil, recently synthesized in Europe, is said to have actions of the peripheral $alpha_1$-receptor inhibition of prazosin and the central postsynaptic alpha-receptor stimulation of clonidine and alpha-methylnorepinephrine (217).

**Beta-adrenergic receptor inhibition.** Soon after introduction of the thiazide compounds, a new series of adrenergic inhibiting drugs was made available that reduced arterial pressure through inhibition of beta-receptor sites (218). However, several years elapsed before the compound propranolol was made available and was shown by Prichard and Gillam (219) to be effective in reducing arterial pressure. Although widely postulated to reduce pressure by "resetting baroreceptors" (220,221), this mechanism has not been substantiated nor has the mechanism that operates through reduced cardiac output (222) or inhibition of renin release from the kidney (99). Patients not responding to beta-adrenergic blocking therapy with a pressure reduction may also have a reduced cardiac output (223), and other patients treated with beta-adrenergic receptor blocking drugs having intrinsic sympathomimetic activity may not demonstrate inhibition of renin release (224). Therefore, like the diuretic agents, the beta-adrenergic receptor blocking agents continue to challenge the investigator for elucidation of a valid antipressor mechanism.

**Vasodilators.** *Calcium inhibitors.* For many years the clinician has been offered a most simplistic explanation for the action of such disparate vasodilators as hydralazine, diazoxide, minoxidil and nitroprusside. These agents have been thought to lower arterial pressure by decreasing vascular smooth muscle tone, but how this is achieved still must be explained. Why only nitroprusside acts on both venules and arterioles remains unexplained. In recent years, a new but inhomogeneous group of the vasodilators has been introduced. Although currently used only for the treatment of angina pectoris in the United States, these so-called slow channel calcium inhibitors act by preventing the intracellular movement of calcium ions from the extracellular space (225). One agent, verapamil, possesses antiarrhythmic activity to slow supraventricular tachycardias (226), but this action is not possessed by the vasodilator nifedipine (227); both actions may be found with diltiazem and nitrendipine (228,229). We may be on the brink of a new era in our understanding of vascular smooth muscle function as our experience with these agents broadens.

**Inhibitors of the renopressor system.** *Captopril.* An active academic intellectual discussion of the 1970s surrounded the practicality of the renopressor system. With the availability of a wide variety of pharmacologic agents that inhibit this system at many levels, the empiric participation of this system in hypertension becomes obvious. Adrenergic inhibiting drugs (including most beta-adrenergic receptor blocking agents) inhibit renin release from the kidney, thereby preventing the formation of angiotensin I from its substrate angiotensinogen. More recently, a second level of inhibition has been achieved with the synthesis of agents that inhibit the angiotensin-converting enzyme, thereby preventing the cleavage of the terminal two amino acids from angiotensin I to form the potent pressor octapeptide angiotensin II. Although several angiotensin-converting enzyme inhibitors have been synthesized, only one such agent is commercially available, captopril; another, enalapril maleate (MK-421), is under active clinical investigation throughout the world (230). At this point, the most logical antihypertensive mechanism is inhibition of the formation of angiotensin II; however, since the angiotensin-converting enzyme is the very

same enzyme that degrades the naturally occurring potent vasodilating agent bradykinin (124), this action also is possible. Furthermore, because angiotensin II stimulates aldosterone production and augments central and peripheral adrenergic outflow to the cardiovascular system, inhibition of these mechanisms is also possible. One additional novel compound capable of inhibiting the renopressor system is saralasin, a sympathetic analog of angiotensin II that competitively inhibits the action of angiotensin II at vascular receptor sites (231).

## Conclusions

Cardiovascular medicine has matured greatly over the past 25 years. To one interested in hypertension, it is clear that the investigation of this major cardiovascular problem has provided its share of knowledge and benefits to humanity. Physicians have moved from a position of passive observation of an elevated arterial pressure to an active role in identifying patients with even mildly elevated pressures in an effort to put into practice that which is now feasible: control of pressure at normotensive levels so that significant improvement of morbidity and mortality can be achieved. This is possible with an impressive array of new diagnostic methods and techniques and a wide variety of pharmacologic agents that can specifically inhibit most naturally occurring mechanisms. Nevertheless, the clues from both older and more recent research augur well for the future of new knowledge and more improved therapy that will continue to bring excitement and satisfaction to the practice of cardiovascular medicine.

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