Historical Trends and Milestones in Hypertension Research
A Model of the Process of Translational Research
Theodore A. Kotchen

“Translation” is a bidirectional research process that often begins with the generation of scientific questions based on clinical observations and subsequently involves the application of basic scientific discoveries into patient care and the community at large. The remarkable history of hypertension-related research reflects the process of translation. The history begins with the development of devices to measure blood pressure, early descriptions of the variability of blood pressure, and recognition by the life insurance industry of the association between blood pressure level and subsequent cardiovascular disease morbidity and mortality. This background has prompted sustained laboratory research efforts aimed at understanding the physiological control of arterial pressure, identifying mechanisms of hypertension, and developing pharmacological agents for the treatment of hypertension. In turn, these initiatives have resulted in clinical trials with hypertensive patients and population-based programs with the goals of more effectively treating and preventing hypertension and its cardiovascular consequences. The purpose of this review is to summarize milestones in this ongoing translation process, a process that has had a considerable impact on patient care and reducing cardiovascular disease morbidity and mortality rates.

Blood Pressure Measurement
The history of hypertension research begins with the development of appropriate techniques for measuring blood pressure. Reverend Stephen Hales is generally credited as being the first person to measure arterial pressure, direct intra-arterial pressure in the horse in 1733. Almost a century later, sphygmographic devices were developed to measure blood pressure noninvasively in humans. The early devices were cumbersome and relatively insensitive. The introduction of the sphygmomanometer into clinical medicine in the late 1800s and early 1900s was accepted by some practitioners as a valuable aid to diagnosis. However, many were initially skeptical, and the British Medical Journal held the view that by using the sphygmomanometer “we pauperize our senses and weaken clinical acuity.”

After Korotkoff’s 1905 landmark description of the sounds associated with the appearance of the pulse wave, there was little change in the measurement of blood pressure in the first half of the 20th century. Toward the end of the 20th century, based primarily on mercury-related health concerns (which many in the field vigorously debated), the mercury manometer has essentially been replaced with aneroid and electronic devices. Mercury is still used for calibrating these devices, and standardized protocols have been recommended to assure their accuracy.

With the increased ability to measure blood pressure, the variability of blood pressure, the influence of physical and emotional stimuli, and the reduction of blood pressure during sleep were recognized by the mid-20th century. In the mid 1940s, Sir Horace Smirk considered it to be clinically useful to distinguish between “basal” and “casual” blood pressure. Basal blood pressure was measured after “emotional desensitization,” which, according to one protocol, consisted of an overnight fast, resting in a quiet warm room for 30 minutes, and then obtaining repeated measurements for an additional 30 minutes. Casual blood pressure consisted of the relatively stable basal blood pressure and a variable supplemental blood pressure. More recently, there has been increased recognition of the prognostic and hypertension management value of home blood pressure and ambulatory blood pressure monitoring, including the importance of day/night blood pressure differences (“dippers” versus “nondippers”).

Identification of Higher Blood Pressure as a Risk Factor
In the United States, the insurance industry provided early and consistent evidence for the clinical significance of higher blood pressures. A few companies began measuring systolic blood pressure in 1906. In 1911, the medical director of the Northwestern Mutual Life Insurance Company wrote, “The sphygmonanometer is indispensable in life insurance examinations, and the time is not far distant when all progressive life insurance companies will require its use in all examinations of applicants for life insurance.”

As techniques for measuring blood pressure improved and increasing evidence for a blood pressure-mortality relationship became apparent, more companies began to require blood pressure measurements of insurance applicants. By 1918, companies were measuring systolic and diastolic blood pressures by auscultation, under somewhat standardized
In a series of reports between 1925 and 1979, the Actuarial Society of America described the population-based distribution of blood pressure, the age-related increases of blood pressure, and the relationships of blood pressure to both body size and mortality. This information was based on >10 million individuals, although data ascertainment was frequently not complete, and the duration of follow-up was relatively short, particularly in the earlier reports. Also, the earlier reports included predominantly white men.

In the 1925 report, among a subsample of 20 000 insured individuals, age 38 to 42 years, the distributions of systolic and diastolic blood pressures were not bimodal (Figure 1). However, this did not necessarily exclude the possibility that those individuals with higher blood pressures may have been omitted because they were denied insurance. The 1925 report also described increasing systolic and diastolic (fifth phase) blood pressures with age in 409,748 men and 51,253 women (Figure 2). At the younger ages, systolic and diastolic blood pressures were lower for women than for men. Pulse pressure also increased progressively with age in both men and women. The report also demonstrated that both systolic and diastolic blood pressures increased with increasing body size in men, defined in terms of “build groups” (average weight for each inch of height) in different age groups of men. However, the report cautioned that “the increase of blood pressure with increasing percentage of overweight is exaggerated” because of the interaction of age with weight in each age group. Based on limited data, the characteristics of blood pressure by body build were similar for women. “Above average” systolic and diastolic blood pressures and pulse pressure were associated with a higher mortality, the only exception being lower mortality in young adults with above average systolic blood pressures: “The ratio of deaths due to organic diseases of the heart, Bright’s disease, cerebral hemorrhage, and apoplexy per 10,000 exposed to risk tended to increase with blood pressure at the older age and usually at the middle ages.” Variations of diastolic blood pressure were of more importance than variations of pulse pressure in predicting mortality.

Because of changing methods for measuring blood pressure and the relatively short period of exposure, the conclusions of the 1925 report were appropriately cautious: “(1) the mortality is lower than the average when systolic or diastolic pressure taken by itself is below the average, but no information is yet available regarding the effect of very low blood pressures; (2) the good effect of a systolic or diastolic pressure slightly below average is likely to be greater at younger than at older ages; (3) mortality increases rapidly with the increase in blood pressure over the average; and (4) substantial departures for the average blood pressure are less significant for pulse pressure than for either systolic or diastolic pressure.”

In a subsequent publication in 1939, the Actuarial Society of American provided more extensive information about the relationship between blood pressure and mortality. Table 1, abstracted from the 1939 report, shows the ratios of actual: expected deaths from cardiovascular and renal diseases, covering 20,210 deaths. For entry ages ≥40, systolic blood

![Figure 1](http://hyper.ahajournals.org/)

**Figure 1.** Percentages of insured individuals with different levels of systolic and diastolic blood pressures. Printed with permission from data compiled by Society of Actuaries, Schaumberg, IL.4(p9)

![Figure 2](http://hyper.ahajournals.org/)

**Figure 2.** Systolic and diastolic blood pressures by age groups among insured individuals. Printed with permission from data compiled by Society of Actuaries, Schaumberg, IL.4(pp11 and 52)
pressure was a more important predictor of death than diastolic blood pressure, and for entry ages <30 years, the influence of diastolic pressure was more marked than systolic pressure. With the exception of low systolic readings at entry ages 10 to 29 years, the prevailing tendency was an increase in mortality ratio with elevation of the systolic reading. For relatively low systolics, the mortality did not advance much as the diastolic increased, but at the middle and higher systolics, mortality mounted rapidly as diastolic readings increased. A combination of low systolic with high diastolic pressure was associated with an increased suicide rate.

The 1959 Build and Blood Pressure Studies again documented the increments of systolic and diastolic blood pressures with age and weight in men and women.6 That report also confirmed a sharp increase in mortality associated with relatively small increases in blood pressure. The rise in mortality was most pronounced for issue ages 30 to 59, and the rise was greater for a given increase in diastolic than for the same increase in systolic pressure. The extra mortality associated with hypertension was less for women than for men, particularly at issue ages ≥40 years.

Conclusions of a subsequent 1979 report of the Society of Actuaries were as described here.7 First, in both men and women, the mortality ratios rose with increase in blood pressure at the time of issue. Second, overweight (35% to 45% above average weight) increased mortality by 20% to 30% of normotensive and borderline hypertensive men and considerably more for men with definite high blood pressure. Increases of mortality among overweight among women were “distinctly smaller” than among overweight men. Third, among insured men with “borderline” hypertension (systolic pressure 140 to 159 mm Hg and diastolic pressure 90 to 94 mm Hg), regardless of treatment, death rates from coronary disease and cerebral hemorrhage were ~50% higher than among normotensive men. Fourth, among insured men with “definite high blood pressures” (systolic ≥160 mm Hg and/or diastolic ≥95 mm Hg), regardless of treatment, compared with normotensive men, death rates from coronary disease and cerebral hemorrhage were more than double; from hypertensive heart disease, >4 times higher; and from kidney disease, approximately double. Excess mortality from these causes increased with the rise in blood pressure. Fifth, among insured men and women treated for blood pressure before issue of their insurance whose blood pressures had been reduced to the normotensive range, the death rates from coronary disease and stroke were virtually normal.

Average blood pressures and the prevalence of both borderline and definite hypertension increased progressively with age in men and women, although, not surprisingly, hypertension prevalence in these insured individuals was considerably lower than that reported in a probability sample drawn from the general population (Health and Nutrition Examination Survey).

A potential criticism of the data in these reports is that it represents only those individuals who applied for and who were issued a life insurance policy. However, subsequent studies from the general population have corroborated and extended the basic conclusions of the insurance reports. For example, the National Health and Nutrition Examination Survey community-based surveys also describe the relationships of blood pressure with age and body size in both women and men, as well as in several racial/ethnic groups. In addition, subsequent studies describe age-related increases of blood pressure from birth to adulthood. Several large cohort studies have demonstrated that relative ranking of blood pressure during childhood tends to be maintained throughout adolescence and into adulthood, suggesting that elevated blood pressure at young ages may be a risk factor for subsequent hypertension in adulthood.8–11

In 1993, the cohort of >350 000 men screened for participation in the Multiple Risk Factor Intervention Trial confirmed a continuous and graded influence of both systolic and diastolic blood pressures on coronary heart disease mortality and end-stage renal disease, extending down to systolic blood pressures of 120 mm Hg.12 In 2001, data from the Framingham Heart Study corroborated the observation that increments in systolic or diastolic blood pressure are associated with incremental increases in mortality.13 In the Framingham study, cardiovascular disease risk increased 2.5-fold in women and 1.6-fold in men with “high normal” blood pressures (systolic blood pressure 130 to 139 mm Hg or diastolic blood pressure 85 to 90 mm Hg). In individuals over age 50 years, both the Multiple Risk Factor Intervention Trial and the Framingham study highlighted the importance of systolic blood pressure and pulse pressure for subsequent cardiovascular and renal disease. Notably, in the Multiple Risk Factor Intervention Trial, the great majority of excess deaths occurred in men with high normal blood pressures (systolic: 130 to 139 mm Hg) or with “stage 1 hypertension” (systolic: 140 to 159 mm Hg).

Although some had suggested that hypertension represented a distinct subset of the population, by 1960 Pickering14 emphasized that hypertension is a “quantitative” and not a “qualitative” trait, meaning that there is a continuous relationship between arterial pressure and mortality over the whole range of arterial pressure: “Arterial pressure is a quantity and its adverse effects are related numerically to it. The dividing line (between normal blood pressure and hypertension) is nothing more than an artifact.”

Consistent with this concept, in a 2002 meta-analysis of 61 prospective studies involving data for 1 million adults, the likelihood of “vascular mortality” (including stroke and ischemic heart disease) was directly related to a “usual” blood pressure down to at least 115/75 mm Hg.15

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### Table 1. Ratios of Actual:Expected Deaths From Cardiovascular and Renal Diseases, by Systolic and Diastolic Blood Pressures, Among Insured Individuals

<table>
<thead>
<tr>
<th>Systolic Reading, mm Hg</th>
<th>Diastolic Reading (Fifth Phase), mm Hg</th>
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<tbody>
<tr>
<td>108 to 132</td>
<td>54 to 78</td>
</tr>
<tr>
<td>133 to 137</td>
<td>79 to 86</td>
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<tr>
<td>138 to 142</td>
<td>87 to 93</td>
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<td>94 to 98</td>
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<tr>
<td>153 to 177</td>
<td>99 to 116</td>
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</table>

Data derived from the Actuarial Society of America.5
Because of the early descriptions of the association of body size with blood pressure, clustering of other risk factors with obesity-related hypertension has become increasingly apparent. Although there have been recent disagreements about specific criteria for a diagnosis of the “metabolic syndrome,” the constellation of related risk factors has been recognized for >80 years. In 1923, Kylin, a Swedish physician, described the association of hypertension with hyperglycemia and gout, and in 1947, Vague drew attention to the association of upper body obesity (android obesity) with type 2 diabetes mellitus and cardiovascular disease. In 1988, Raven described “syndrome X” as (1) resistance to insulin-stimulated glucose uptake; (2) glucose intolerance; (3) hyperinsulinemia; (4) increased very low-density lipoprotein triglycerides; (5) decreased high-density lipoprotein cholesterol; and (6) hypertension. He described relationships among these variables and suggested that insulin resistance is the basic underlying abnormality. This syndrome has been observed in many populations and in both children and adults. Defining the pathophysiology of the relationships among central obesity, insulin resistance, and hypertension continues to be an active area of laboratory and clinical research.

Evolving Concepts of the Pathophysiology of Hypertension

Recognition of the variability of blood pressure within a population and the increasing evidence for the clinical significance of higher blood pressures provoked a still-continuing search for the causes of hypertension. In 1844, Richard Bright, a physician-pathologist at Guy’s Hospital in London, attributed hypertension to intrinsic renal disease. Subsequent observations by Fred Mahomed (1874), Clifford Allbutt (1896), Henri Huchard (1893), and others demonstrated that hypertension may occur without overt renal disease and may precede arteriosclerosis. Both Mahomed and Otto Frank (1911) have been credited for coining the term “essential hypertension.” This term implied that the elevation of blood pressure was a compensatory reaction to overcome ischemia of the tissue caused by constricted arterioles. In a 1912 address before the Glasgow Southern Medical Society, Sir William Osler21 made the following statement about high blood pressure being a compensatory reaction to overcome ischemia of the tissue caused by constricted arterioles.

In 1972, Brunner et al emphasized that hypertension is not a single disease but a heterogenous group of disorders with discrete etiologies. Based on the relationship of plasma renin activity to 24-hour urine sodium excretion, compared with normotensive individuals, they observed that ≈30% of hypertensives have low renin and 20% have high renin (Figure 5). This was felt to reflect 2 forms of vasoconstriction in essential hypertension, a renin angiotensin–mediated vasoconstriction (high renin) and a volume-mediated vasoconstriction (low renin). They further pointed out that patients with high renin hypertension were at greater risk for cardiovascular events than low renin patients and that the preferred therapies for high- and low-renin patients were renin-angiotensin blockers and diuretics (or calcium channel blockers), respectively.

Figure 3. Page’s mosaic theory of hypertension. Reproduced with permission from Elsevier.24(p915)

Islands societies with low levels of acculturation, there were no age-related increases of blood pressure in both men and women. In these and other acculturated societies, historically, the occurrence of cardiovascular disease was strikingly absent. A low salt intake may have been one important environmental factor.

In 1949, Page introduced the concept of a “mosaic theory” to explain the etiology of hypertension (Figure 3). By this he meant that “… most of the known and probably many unknown control factors could be accommodated as long as they were in equilibrium, maintain blood pressure and tissue perfusion at relative constancy, but still adapting to tissue needs. Essential hypertension was designated a disease of control or regulation, and no constant dominant cause could be expected except in the secondary hypertension.”

Beginning in 1967, Guyton described a “hierarchy of pressure control systems” that provides both short-term damping and long-term control of arterial pressure. He hypothesized that short-term (cardiovascular reflexes) and intermediate-term (capillary fluid shifts, vascular compliance, and hormones) control mechanisms function primarily as pressure-buffering mechanisms and that long-term control of pressure is vested almost entirely in the long-term control of body fluid volumes, primarily by the kidney (Figure 4).
Mechanisms of hypertension were more readily identifiable with the discoveries of secondary forms of hypertension. Pheochromocytoma was the first known cause of curable hypertension. Frankel described the symptoms and the tumor of the adrenal gland in 1886, and in 1922, Labbe et al provided a complete description of the disease and its pathophysiology. In 1926, Roux performed the first surgical resection of a pheochromocytoma in Lausanne, Switzerland, and later in the same year Mayo performed the first surgical resection in the United States.

Goldblatt et al designed a clamp to constrict the renal artery of the dog, and in 1932 he demonstrated that unilateral (and bilateral) renal artery constriction produced hypertension. Hypertension was reversed either by removal of the clamp or unilateral nephrectomy. Several decades earlier, in 1898, Tigerstedt and Bergman had demonstrated that the injection of a crude saline extract of rabbit kidneys into other rabbits raised the arterial pressure. They named the pressor substance in the kidney extract “renin.” It was subsequently determined that renin was the hypertension-producing factor released by the clamped, ischemic kidney. After Goldblatt’s observations in the dog, physicians searched for this disorder in hypertensive patients. Clinically, most patients had either arteriosclerotic disease or, in younger patients, fibromuscular dysplasia. Based on kidney size and/or degree of narrowing of the renal artery, between 1940 and 1960, a large number of...
nephrectomies were performed with a low cure rate. Subsequent
evaluations to determine the functional significance of a
stenotic lesion included split-renal function tests and deter-
mination of the renal vein:renin ratio. Over time, unilateral
nephrectomy was largely replaced by renal revascularization
and, more recently, by stenting of the obstructed renal artery.
However, with the introduction of effective antihypertensive
agents, it has become apparent that hypertension can be
controlled and renal function preserved in many of these
patients with drug therapy. Clinical trials comparing outcomes
do not provide sufficient evidence of antihypertensive drugs.

In 1932, Cushing described a group of 12 cases, all young
adults, with the following clinical manifestations: rapidly
acquired adiposity confined to face, neck and trunk; dusky or
plethoric appearance of the skin with purplish striae; in-
creased growth of hair on face and trunk; tendency of loss of
stature and kyphosis; amenorrhea in the female and impo-
tence in the male; raised arterial pressure; backache and
abdominal pain; and fatigue and weakness. Cushing thought
that all of the clinical evidence of this syndrome was caused
by a small basophil adenoma of the pituitary. However, it was
subsequently discovered that the pituitary disorder resulted in
bilateral adrenal hyperplasia and that the clinical manifesta-
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subsequently discovered that the pituitary disorder resulted in
bilateral adrenal hyperplasia and that the clinical manifesta-
tions of the syndrome, including hypertension, were related to
excess cortisol production by the adrenal stimulated by
pituitary adrenocorticotropic hormone.

In 1955, Conn described a single patient with hyperten-
sion, muscle weakness, polyuria, and serum K+ +1.6 mEq/L.
Electrocardin, a sodium-retaining steroid, had been identified
recently in urine and renamed aldosterone. In Conn’s patient,
assay of the urine for this steroid was positive. Urinary
17-hydroxysteroid and 17-keto steroid excretions were normal.
The right adrenal containing an adenoma was subse-
quent removed, and 6 months after surgery her blood
pressure was 120/80 mm Hg. Continuing debate about the
prevalence of primary aldosteronism depends on the intensity
of screening and the selection of patient groups. In addition,
we now know that 30% of patients with primary aldoste-
ronism have bilateral adrenal hyperplasia rather than a dis-
crete adrenal tumor, and these patients are generally not
considered surgical candidates. Curiously, in patients with
bilateral hyperplasia, hypertension may persist even after
bilateral adrenalectomy.

Surgical Treatments of Essential Hypertension
For a brief period, surgical therapies were undertaken even in
the absence of an identifiable secondary cause of hyperten-
sion. Based on the presumption that high pressure was
attributed to overaction of the sympathetic nerves, various
approaches to surgical sympathectomy were undertaken.
Results of several series were reported in the late 1940s and
early 1950s. Hammarstrom and Bechgaard and Smithwick
reported that sympathectomy improved the expectation of
life. However, as summarized by Pickering, “Sympathecto-
my has in general a limited effectiveness in reducing arterial
pressure and is much inferior to drug treatment. It can, in a
few patients, have a spectacular effect. The difficulty is to
know which.” Furthermore, these were painful, debilitating
operations that were justified only in severe hypertension.
Nevertheless, surgical sympathectomy stimulated the develop-
ment of drugs that inhibited the sympathetic nervous system by blocking transmission of sympathetic nerve activ-
ity through the autonomic ganglia. In the 1950s, partial or
total adrenalectomies, sometimes in combination with symp-
pathectomy, were also carried out in selected patients with
severe hypertension, and with availability of cortisone, total
adrenalectomy seemed less fearful. However, these surgical
procedures rapidly became superseded by the discovery and
increasing availability of antihypertensive drugs.

Drug Development and Clinical Trials
Despite the increasing evidence for the association of cardio-
vascular disease and mortality with blood pressure, there
were skeptics in the medical community and in the lay press
about the imperative to lower blood pressure. In 1931, Dr
Paul Dudley White, an eminent Boston cardiologist wrote:
“Hypertension may be an important compensatory mecha-
ism which should not be tampered with, even were it certain
that we could control it.”

Also, in 1931, Hay stated in the British Medical Journal
that, “The greatest danger to a man with high blood pressure
lies in its discovery, because then some fool is certain to try
and reduce it.”

In the 1946 edition of Tice’s Practice of Medicine (one of the
leading textbooks of Medicine at the time), Scott advised:
May not the elevation of systemic blood pressure be a
natural response to guarantee a normal circulation to
the heart, brain and kidneys (‘essential’ hyperten-
sion). Overzealous attempts to lower the pressure
may do no good and often do harm. Many cases of
essential hypertension not only do not need any
treatment but are much better off without it.

The landmark Veterans Administration Cooperative Stud-
ies, largely designed and supervised by Dr Edward Freis,
provided early clinical trial evidence for the beneficial impact
of lowering blood pressure with antihypertensive agents. In a
placebo-controlled trial, active drug treatment in patients with
diastolic blood pressures 115 to 129 mm Hg resulted in a
decrease in stroke, aortic dissection, and malignant
hypertension within 2 years. Follow-up was terminated
prematurely in the placebo-treated patients (15.7 versus 20.7
months in controls) because of a higher incidence of ter-
minal events. A subsequent Veterans Administration
placebo-controlled trial demonstrated the benefit of antihy-
pertensive drug treatment of patients with diastolic blood
pressures 90 to 114 mm Hg, especially patients with diastolic
blood pressures $\geq 105$ mm Hg. The 2 studies were pub-
lished in 1967 and 1970, respectively, and the antihyperten-
The incidence of stroke by lowering diastolic blood pressure with drug treatment reduced the rate up to that time strongly supported the conclusion that lower-"mild" hypertension. By 1990, meta-analyses of various trials evaluated the benefits of antihypertensive therapy in patients with hypertension in Europe. More recent trials have evaluated lower blood pressure targets for hypertension control (eg, Hypertension Action to Control Cardiovascular Risk in Diabetes Trial, Blood Pressure Intervention Trial, is designed to test whether reducing systolic blood pressure to <120 mm Hg compared with a target of <140 mm Hg will reduce cardiovascular disease risk.

Based on pooling results from clinical trials, meta-analyses suggest essentially equivalent blood pressure-lowering effects of the following 6 major classes of drugs when used as monotherapy: diuretics, β-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium antagonists, and α1 receptor blockers. However, clinical trial results have suggested that there are subgroup differences in responses (eg, diuretics for low renin patients and renin-angiotensin blockers for high renin patients). In addition, coincident with the development and increasing availability of newer antihypertensive agents in the 1970s and 1980s, trials were designed to evaluate the possibility that different classes of antihypertensive agents vary in their capacity to decrease cardiovascular and renal disease, independent of their ability to lower blood pressure. Most trials have failed to show significant differences in cardiovascular outcomes with different drug regimens, as long as equivalent decreases in blood pressure were achieved. However, in specific patient groups, relatively recent trial results suggest that converting enzyme inhibitors and angiotensin receptor blocking agents have advantages beyond that of blood pressure control in reducing adverse cardiovascular events in high-risk patients (eg, Heart Outcomes Prevention Evaluation, Losartan Intervention for Endpoint Reduction in Hypertension, and European Trial on Reduction of Cardiac Events With Perindopril in Stable Coronary Artery Disease) and renal outcomes in diabetic patients.

**Trials of Lifestyle Interventions**

The earliest comment that relates dietary salt to blood pressure is that of Huang Ti Nei Ching Su Wein (≈2600 BC) from the translation by Wan Ping (AD 762), "... therefore if large amounts of salt are taken, the pulse will stiffen or harden." In 1905, 2 French medical students, Ambard and Beaujard, were the first to promote the concept that the cause of hypertension was salt in the diet, and they claimed some success in reducing blood pressure by restricting salt. They thought the culprit was chloride. Chloride was readily measured by the silver nitrate method; the flame photometer had not been invented. Interest in chloride has been rekindled by the recent demonstration that sodium salts composed of anions other than chloride have relatively little impact on blood pressure.

Subsequent attempts to restrict salt as a strategy for the treatment of hypertension met with either limited success or without careful documentation of its impact on blood pressure until the mid-1940s. In 1948, Kempner renewed interest in salt restriction with his introduction of the rice-fruit diet, which contained 150 mg of sodium per day. In 322 of 500 patients with hypertensive vascular disease, the diet...
produced one or more of the following: decrease of mean arterial pressure $>20$ mm Hg; reduction in heart size; reversal of T wave inversions on ECG; and disappearance of severe retinopathy. However, as described by Pickering, the diet did not have widespread acceptability: “It is insipid, unappealing and monotonous and demands great care its preparation, for if the salt rises above 250 mg/d, the effect in most instances is lost.”

Over the past 25 years, a number of controlled, clinical trials have documented the benefits of reduction of salt...
areas of research that were likely to result in new knowledge about mechanisms of hypertension; (2) to identify promising hypertension research at that time. The objectives of the task (NHLBI) established a Hypertension Task Force, chaired by

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statement about the regulation of arterial pressure74(p9): “Blood

Almost a century ago, a review of the developing methodologies

Table 4. Examples of Nonpharmacologic Trials for the
Prevention or Treatment of Hypertension

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dietary Intervention Study for Hypertension (DiShy)66</td>
<td>1985</td>
<td>Weight loss and salt restriction more than doubled success in withdrawal of drug therapy in patients with mild hypertension</td>
</tr>
<tr>
<td>Trial of Antihypertensive Intervention Management (TAIM)67</td>
<td>1991</td>
<td>In the short term, drugs outperformed diet and weight loss in the treatment of mild hypertension</td>
</tr>
<tr>
<td>Trials of Hypertension Prevention (TOHP): Phase I68*</td>
<td>1992</td>
<td>In the short term, weight reduction and, to a lesser extent sodium reduction lowered blood pressure in persons with high normal blood pressures; blood pressure was not reduced by either stress management or nutritional supplements</td>
</tr>
<tr>
<td>Trial of Stress Reduction69</td>
<td>1995</td>
<td>In the short term, transcendental meditation lowered blood pressure in older blacks with mild hypertension</td>
</tr>
<tr>
<td>Dietary Approaches to Stopping Hypertension (DASH)70*</td>
<td>1997</td>
<td>A diet rich in fruits, vegetables, and low-fat dairy products substantially reduced blood pressure in adults with high normal blood pressures or mild hypertension</td>
</tr>
<tr>
<td>Trial of Nonpharmacologic Interventions in the Elderly (TONE)71*</td>
<td>1998</td>
<td>Weight loss and reduced sodium intake each safely lowered blood pressure in older persons with hypertension</td>
</tr>
<tr>
<td>Trials of Hypertension Prevention (TOHP): Phase II72*</td>
<td>2001</td>
<td>Clinically significant long-term reductions of blood pressure were achieved with modest reductions of weight loss</td>
</tr>
<tr>
<td>PREMIER Trial73*</td>
<td>2003</td>
<td>Individuals with above-normal blood pressure, including stage 1 hypertension, can make multiple lifestyle changes that lower blood pressure and reduce cardiovascular disease risk</td>
</tr>
</tbody>
</table>

*This study was funded by the National Heart, Lung and Blood Institute.

intake, other nutritional interventions, stress reduction, weight loss, and other lifestyle modifications on the prevention and treatment of hypertension. Several of these trials are listed in Table 4.66–73

Basic and Translational Research

Almost a century ago, a review of the developing methodologies for measuring blood pressure and of information about blood pressure variability and its significance contained the following statement about the regulation of arterial pressure74(p9): “Blood pressure is a matter of the internal secretions … It is beyond question that one if not more of the internal secretions has the power to goad blood pressure to instant response to the cells of organs and tissues of the body for nutrition, though just how it acts is still shrouded in impenetrable mystery.”

In 1975, the National Heart, Lung and Blood Institute (NHLBI) established a Hypertension Task Force, chaired by Drs Harriet Dusman and Edward Frohlich, to assess the state of hypertension research at that time. The objectives of the task force were as follows: (1) to summarize current knowledge about mechanisms of hypertension; (2) to identify promising areas of research that were likely to result in new knowledge leading to better control and prevention of high blood pressure; and (3) to assess future research needs in the field of hypertension.

In 1979, the task force produced a 9 volume report outlining the public health problem of hypertension and identified the following research areas that merited particular emphasis73: (1) the role of sodium in the activity of vascular smooth muscle and in the regulation of fluid volumes, hormonal systems, nervous system function, and blood pressure; (2) the function of the nervous system, especially the central nervous system, in the regulation of normal arterial pressure and pathogenesis and treatment of hypertension; (3) the influence of local modulators of resistance (eg, renin-angiotensin, kallikrein-kinin, and prostaglandins) on blood pressure; (4) the role of the microcirculation and veins in the development and maintenance of hypertension; (5) the study of blood pressure regulation, hypertension, and antihypertensive therapy during growth and development of the child; (6) genetic mechanisms of hypertension; and (7) mechanisms responsible for the changes in small arteries and arterioles that cause the increase in total peripheral resistance of chronic hypertension.

The task force also developed recommendations for the use of animal models for hypertension-related research, for manpower training needs, and for resources and technology needs related to hypertension research and patient care. All of these recommendations were intended to serve as a platform for future federal funding.

The NHLBI has continued to periodically create task forces and convene working groups to develop recommendations for funding priorities for specific hypertension-related topics. For example, in 2008, the NHLBI convened a working group on target organ damage in hypertension, chaired by Drs David Harrison and Ernesto Schiffrin. The objectives were to identify new research directions that elucidate the basic biophysical and biological mechanisms underlying organ damage in hypertension and that lead to the development of preclinical and presymptomatic markers of organ damage to allow early treatment decisions with the goal of attenuating or preventing organ damage. Between 1981 and 2007, NHLBI annual support for hypertension-related research progressively increased from $80.6 million to $211.1 million. NHLBI support for years 2008, 2009, and 2010 was $167.4, $169.8, and $147.7 million, respectively. In part, a change in National Institutes of Health–wide methodology for calculating dollars associated with a particular disease may have contributed to the apparent funding decrease in 2008–2010.

As one approach to highlighting outstanding research accomplishments over the past 45 years, Table 5 lists recipients of the American Heart Association Council for High Blood Pressure Research annual award for outstanding research, beginning at the time of the introduction of this award in 1966. The purpose of the award is to recognize scientists “who have had a major impact in the field of hypertension and whose research has contributed to improved treatment and greater understanding of high blood pressure.”

Although not the exclusive arbiter of meritorious research, the spectrum of discoveries recognized by the Council for High Blood Pressure Research over the past 4.5 decades
Table 5. Recipients of the Annual Council for High Blood Pressure Research Award for Outstanding Research

<table>
<thead>
<tr>
<th>Year</th>
<th>Recipient(s)</th>
<th>Discovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>1966</td>
<td>Harry Goldblatt, MD</td>
<td>In the dog, demonstrated that impairment of renal blood flow resulted in secretion of a renal pressor substance and hypertension that was reversible with restoration of renal blood flow</td>
</tr>
<tr>
<td></td>
<td>Ernst Klenk, MD</td>
<td>(1) Studied biochemistry of lipids and fatty acids; (2) described and isolated cerebrosides from brain; (3) elucidated structure of sphingosine; (4) purified and described structure of gangliosides</td>
</tr>
<tr>
<td>1967</td>
<td>Peter Holtz, MD</td>
<td>(1) Discovered dopamine, the precursor of norepinephrine; (2) showed that norepinephrine is synthesized by nerve tissue and adrenal medulla and that it is excreted in urine</td>
</tr>
<tr>
<td></td>
<td>US Von Euler, MD</td>
<td>(1) Demonstrated that norepinephrine transmits the message from sympathetic neurons to tissues; (2) studies of urinary excretion of norepinephrine led to diagnostic test for pheochromocytoma; (3) prostaglandin discovered in his laboratories</td>
</tr>
<tr>
<td></td>
<td>John W. Cornforth, MD</td>
<td>Determined the chemical pathway for the biosynthesis of cholesterol</td>
</tr>
<tr>
<td></td>
<td>George J. Popjak, MD</td>
<td>Determined the chemical pathway for the biosynthesis of cholesterol</td>
</tr>
<tr>
<td>1968</td>
<td>F. Merlin Bumpus, PhD</td>
<td>Proved angiotensin’s structure by synthesis</td>
</tr>
<tr>
<td></td>
<td>Robert Schweitzer, PhD</td>
<td>Proved angiotensin’s structure by synthesis</td>
</tr>
<tr>
<td></td>
<td>W. Stanley Peart, MD</td>
<td>Determined angiotensin’s amino acid sequence</td>
</tr>
<tr>
<td></td>
<td>Leonard T Skeggs, Jr, PhD</td>
<td>Described precursor-effector relationships between angiotensinogen and angiotensin I and II</td>
</tr>
<tr>
<td>1969</td>
<td>Jerome W. Conn, MD</td>
<td>Described a new syndrome, an aldosterone-producing adrenal cortical tumor as a cause of human hypertension</td>
</tr>
<tr>
<td></td>
<td>Jaques Genest, MD</td>
<td>Determined that aldosterone was linked to renin by demonstrating that its secretion was regulated by angiotensin II</td>
</tr>
<tr>
<td></td>
<td>Franz Gross, MD</td>
<td>Determined that aldosterone was linked to renin by demonstrating that its secretion was regulated by angiotensin II</td>
</tr>
<tr>
<td></td>
<td>John H. Laragh, MD</td>
<td>Determined that aldosterone was linked to renin by demonstrating that its secretion was regulated by angiotensin II</td>
</tr>
<tr>
<td>1970</td>
<td>Irvine H. Page, MD</td>
<td>Deduced that renin was an enzyme that acted on a substrate to generate a third substance, that he named angiotensin; Braun-Menendez in Argentina identified the same substance and named it hypertensin; the 2 names were combined to angiotensin</td>
</tr>
<tr>
<td></td>
<td>Sir George Pickering, MD</td>
<td>Seminal observations regarding the regulation of arterial pressure and the natural history of hypertension</td>
</tr>
<tr>
<td>1972</td>
<td>John L. Oncley, MD</td>
<td>Measured and characterized serum lipoproteins in human health and disease</td>
</tr>
<tr>
<td></td>
<td>John W. Gofman, MD</td>
<td>(1) Identified 3 major classes of lipoproteins: low-density lipoprotein (LDL), very low-density lipoprotein (VLDL), and high-density lipoprotein (HDL); (2) demonstrated that high LDL and low HDL are risk factors for coronary heart disease</td>
</tr>
<tr>
<td></td>
<td>Robert S. Gordon, MD</td>
<td>Discovered the metabolic importance of plasma fatty acid transport</td>
</tr>
<tr>
<td></td>
<td>Vincent P. Dole, MD</td>
<td>Discovered the metabolic importance of plasma fatty acid transport</td>
</tr>
<tr>
<td>1975</td>
<td>Lewis K. Dahl, MD</td>
<td>Demonstrated the crucial role of sodium chloride in human hypertension and in animal models in which there are sensitizing genetic and renal factors</td>
</tr>
<tr>
<td></td>
<td>James O. Davis, MD</td>
<td>(1) Demonstrated that the adrenal cortex, through hypersecretion of aldosterone, plays an important role in edematous states; (2) showed that renin plays a dominant role in the production of angiotensin II; (3) clarified the role of the anterior pituitary in control of aldosterone secretion; (4) clarified the contributions of renal perfusion pressure, renal tubular mechanisms, and prostaglandins in the control of renin release</td>
</tr>
<tr>
<td></td>
<td>Walter Kempner, MD</td>
<td>(1) Developed the rice diet (low in calories, NaCl, and protein) for the treatment of hypertension, heart failure, obesity, renal failure, and diabetes mellitus; (2) demonstrated the effect of the rice diet in reversing malignant hypertension</td>
</tr>
<tr>
<td>1976</td>
<td>Raymond P. Ahlquist, PhD</td>
<td>Identified and defined the functional significance, and named 2 different post ganglionic receptors, α and β adrenergic receptor antagonists</td>
</tr>
<tr>
<td></td>
<td>James W. Black, FRS</td>
<td>Developed jaundecine diuretics</td>
</tr>
<tr>
<td>1977</td>
<td>James F. Tait, FRS</td>
<td>(1) Identified and provided structural analysis of aldosterone (initially named electrocortin); (2) measured the effects of adrenal hormones on mineral metabolism</td>
</tr>
<tr>
<td></td>
<td>Sylvia A. S. Tait, FRS</td>
<td>(1) Identified and provided structural analysis of aldosterone (initially named electrocortin); (2) measured the effects of adrenal hormones on mineral metabolism</td>
</tr>
<tr>
<td></td>
<td>John S. Luetscher, MD</td>
<td>Implicated aldosterone as playing a major role in heart failure, nephrosis, and sodium depletion</td>
</tr>
<tr>
<td>1978</td>
<td>Louis Tobian, Jr, MD</td>
<td>(1) Demonstrated the importance of prostaglandins, renin, renal papillary blood flow, sodium, and potassium in the pathogenesis of hypertension; (2) demonstrated a protective effect of potassium on stroke</td>
</tr>
<tr>
<td></td>
<td>Karl H. Beyer, Jr, MD</td>
<td>Developed chlorothiazide diuretics</td>
</tr>
<tr>
<td></td>
<td>James M. Sprague, PhD</td>
<td>Developed chlorothiazide diuretics</td>
</tr>
<tr>
<td>1980</td>
<td>Blomm U. G. Folkow, MD, PhD</td>
<td>(1) Contributed to an understanding of the role of the nervous system in the control of vascular tone; (2) contributed to an understanding of the central nervous system, renin-angiotensin-aldosterone axis, adrenoconstrictor hormone-glucocorticoid and anti-diuretic hormone activities that affect blood pressure during stress</td>
</tr>
<tr>
<td></td>
<td>Arthur C. Guyton, MD</td>
<td>Pioneered the application of large-scale systems analyses to model cardiovascular regulation</td>
</tr>
<tr>
<td>1981</td>
<td>Edward D. Freis, MD</td>
<td>Demonstrated the value of drug treatment of hypertension in altering prognosis</td>
</tr>
<tr>
<td></td>
<td>William B. Kannel, MD</td>
<td>Documented the cardiovascular risks of higher blood pressures (Framingham study)</td>
</tr>
</tbody>
</table>

(Continued)
<table>
<thead>
<tr>
<th>Year</th>
<th>Recipient(s)</th>
<th>Discovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>1982</td>
<td>Kyuzo Aoki, MD</td>
<td>Jointly established the following rat models of hypertension: the spontaneously hypertensive rat (SHR), the stroke-prone SHR (SHRSP), and the malignant SHR (M-SHRSP)</td>
</tr>
<tr>
<td></td>
<td>Koze Okamoto, MD</td>
<td>Jointly established the following rat models of hypertension: the SHR, the SHRS, and the M-SHRSP</td>
</tr>
<tr>
<td></td>
<td>Yukio Yamori, MD</td>
<td>Jointly established the following rat models of hypertension: the SHR, the SHRS, and the M-SHRSP</td>
</tr>
<tr>
<td>1983</td>
<td>Sergio Henrique Ferreira, MD, PhD</td>
<td>Found that snake venom peptides inhibited an enzyme that degraded bradykinin and that also converted the prohormone angiotensin I to the active hormone, angiotensin II</td>
</tr>
<tr>
<td></td>
<td>Miguel A. Ondetti, PhD</td>
<td>Converted Ferreira's discovery into a practical drug, captopril</td>
</tr>
<tr>
<td></td>
<td>David Cushman, PhD</td>
<td>Converted Ferreira's discovery into a practical drug, captopril</td>
</tr>
<tr>
<td>1984</td>
<td>David F. Bohr, MD</td>
<td>(1) Described mechanisms of vascular smooth muscle contraction; (2) described the contribution of the vasculature to the development of hypertension</td>
</tr>
<tr>
<td>1985</td>
<td>Pierre Corvol, MD</td>
<td>Inferred structure of renin from its RNA sequence, using the technology of DNA cloning</td>
</tr>
<tr>
<td></td>
<td>Joel Menard</td>
<td>Inferred structure of renin from its RNA sequence, using the technology of DNA cloning</td>
</tr>
<tr>
<td></td>
<td>Tadashi Inagami, PhD</td>
<td>Purified and produced a complete structure of the renin molecule, using latest protein-sequencing methods</td>
</tr>
<tr>
<td>1986</td>
<td>John C. McGiff, MD</td>
<td>Described the contributions of eicosanoids to the regulation of vascular tone and renal function</td>
</tr>
<tr>
<td></td>
<td>Maurice B. Burg, MD</td>
<td>Described mechanisms by which cells in the renal medulla withstand the high concentrations of NaCl and urea that occur there when the kidney produces concentrated urine</td>
</tr>
<tr>
<td>1987</td>
<td>Donald Reis, MD</td>
<td>(1) Demonstrated the capacity of the brain to regulate the peripheral circulation and its own blood flow; (2) established the importance of the nucleus tractus solitarius for regulation of arterial pressure</td>
</tr>
<tr>
<td>1988</td>
<td>Robert R. Furchgott, PhD</td>
<td>(1) Discovered that endothelium modulates vascular tone and mediates relaxation of vascular smooth muscle produced by neurotransmitters, hormones, and pharmacological agents; (2) demonstrated that relaxation results from release of a labile factor from stimulated endothelial cells, a factor he called endothelium-derived relaxing factor (EDRF)</td>
</tr>
<tr>
<td></td>
<td>Fred Murad, MD, PhD</td>
<td>(1) Uncovered the cellular mechanisms linking cyclic nucleotides to the vasodilator properties of endothelial-derived relaxing factors, atrial natriuretic peptide, and other vasoactive stimuli; (2) defined the role of nitric oxide in regulating vascular function, blood pressure, heart function, and other body functions</td>
</tr>
<tr>
<td>1989</td>
<td>Edgar Haber, MD</td>
<td>(1) Developed antibody for angiotensin and radioimmunoassay for renin activity; (2) purified human and canine renin and developed renin antibodies; (3) utilized renin antibodies and a synthetic renin inhibitor to evaluate renin’s role in blood pressure regulation</td>
</tr>
<tr>
<td>1990</td>
<td>Francois M. Abboud, MD</td>
<td>(1) Studied the neural regulation of the circulation; (2) described cellular and molecular mechanisms of mechanical activation of baroreceptor neurons; (3) described integrated control of sympathetic nerve activity in physiological and pathological states</td>
</tr>
<tr>
<td></td>
<td>Michael J. Brody, PhD</td>
<td>(1) Helped to define the role of the autonomic nervous system, including the hypothalamus, in contributing to hypertension; (2) defined the role of autacoids (eg, histamine and prostaglandins) and angiotensin II in modulating sympathetic activity</td>
</tr>
<tr>
<td>1991</td>
<td>Salomon Z. Langer, MD</td>
<td>(1) Discovered presynaptic inhibitory α-adrenoceptors on noradrenergic nerve terminals and identified their role in modulating noradrenaline release during nerve stimulation; (2) characterized pharmacological differences between α1- and α2-adrenoceptors; (3) discovered and developed clinically useful adrenoceptor antagonists</td>
</tr>
<tr>
<td></td>
<td>Andrew P. Somlyo, MD</td>
<td>(1) Identified mechanisms that regulate contraction of smooth muscle, independent of the membrane potential; (2) demonstrated that actin-myosin interactions are responsible for force generation in smooth muscle</td>
</tr>
<tr>
<td></td>
<td>Avril V. Somlyo, PhD</td>
<td>(1) Identified mechanisms that regulate contraction of smooth muscle, independent of the membrane potential; (2) demonstrated that actin-myosin interactions are responsible for force generation in smooth muscle</td>
</tr>
<tr>
<td>1992</td>
<td>Detlev Ganten, MD, PhD</td>
<td>Elucidated fundamental mechanisms of the pathophysiology and molecular biology of hypertension, including the renin-angiotensin system</td>
</tr>
<tr>
<td>1993</td>
<td>John Paul Rapp, DVM, PhD</td>
<td>(1) Developed a paradigm for genetic analyses of blood pressure in the rat; (2) provided insights and direction for the genetic investigation of hypertension</td>
</tr>
<tr>
<td>1994</td>
<td>Adalio J. DeBold, OC, PhD</td>
<td>Discovered that the heart produces atrial antinatriuretic factor (ANF)</td>
</tr>
<tr>
<td></td>
<td>Ervin G. Erdos, MD</td>
<td>(1) Defined critical enzymes involved in the metabolism of peptides that regulate blood pressure; (2) determined that angiotensin I-converting enzyme (ACE) and kininase II are identical enzymes, an observation that facilitated the development of ACE inhibitors</td>
</tr>
<tr>
<td>1995</td>
<td>Louis J. Ignarro, PhD</td>
<td>(1) Discovered that nitric oxide (NO) is produced by blood vessels and controls blood flow; (2) demonstrated that deficiency of NO leads to cardiovascular disease</td>
</tr>
<tr>
<td></td>
<td>Salvador Moncada, MD, PhD</td>
<td>(1) Described the structure of prostacyclin; (2) demonstrated that endothelium derived relaxing factor is nitric oxide</td>
</tr>
<tr>
<td>1996</td>
<td>Robert J. Lefkowitz, MD</td>
<td>(1) Cloned adrenergic receptors, elucidated their molecular mechanisms of action, and described their role in the control of cardiovascular homeostasis; (2) described the importance of phosphorylation for the regulation of adrenergic receptor function</td>
</tr>
<tr>
<td></td>
<td>Oliver Smithies, PhD</td>
<td>(1) Used homologous recombination to insert altered genes into specific positions in DNA of living cells; (2) applied this technique to transfer “designer mutations” to living animals to study high blood pressure and cardiovascular disease</td>
</tr>
</tbody>
</table>

(Continued)
<table>
<thead>
<tr>
<th>Year</th>
<th>Recipient(s)</th>
<th>Discovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>1997</td>
<td>Oscar A. Carretero, MD</td>
<td>(1) Demonstrated that renal kinins are involved in the regulation of sodium and water excretion; (2) contributed to the understanding of the role of vasopressor and vasodepressor hormones and autacoids in the regulation of arterial pressure, renal function, and hypertension; (3) showed that kinins contribute to the effect of ACE inhibitors</td>
</tr>
<tr>
<td>1998</td>
<td>Gerald F. Dibona, MD</td>
<td>(1) Described the role of the renal nerves in control of renal function (renin secretion, sodium excretion, and renal blood flow); (2) demonstrated that increased neural activity to the kidneys limits their ability to excrete sodium</td>
</tr>
<tr>
<td>1999</td>
<td>Victor J. Dzau, MD</td>
<td>(1) Quantified the relative importance of neurohormonal controllers in the short-term and long-term control of arterial pressure; (2) pioneered techniques for chronic instrumentation and monitoring hemodynamic data in unanesthetized dogs and rats; (3) contributed to the understanding of the role of the kidney, especially the renal medulla, in the long-term regulation of arterial pressure, with emphasis on vasopressin, renin-angiotensin-aldosterone, and NO</td>
</tr>
<tr>
<td>2000</td>
<td>Haralambos Gavras, MD</td>
<td>(1) Demonstrated in experimental animals and human hypertensives, the capacity of angiotensin II receptor blockers and ACE inhibitors to lower blood pressure; (2) helped elucidate pathogenic mechanisms, hemodynamic responses, and hormonal patterns in hypertension, ischemic heart disease, and heart failure and the role of blocking the renin-angiotensin system in treating these abnormalities</td>
</tr>
<tr>
<td>2001</td>
<td>Hans R. Brunner, MD</td>
<td>(1) Observed that angiotensin II is a risk factor for cardiovascular complications in hypertensive patients; (2) conducted pioneering studies (with Gavras) to investigate the role of angiotensin II antagonists and ACE inhibitors in experimental animals and humans with hypertension</td>
</tr>
<tr>
<td>2002</td>
<td>Jay Cohn, MD</td>
<td>(1) Demonstrated benefits of vasodilator therapy in patients with left ventricular failure; (2) explored the role of neurohumoral factors in congestive heart failure and demonstrated a direct relationship between mortality and plasma norepinephrine (served as the basis for β-blocker therapy in heart failure)</td>
</tr>
<tr>
<td>2003</td>
<td>Victor J. Dzau, MD</td>
<td>(1) Purified renin and developed monoclonal antibodies that enabled direct assay of renin; (2) cloned the angiotensin II type 2 receptor gene and found that the angiotensin II type 2 receptor is antagonistic to the angiotensin II type 1 receptor; (3) elucidated the importance of renin-angiotensin as a mediator of tissue function and pathology; (4) demonstrated the efficacy of NO synthetase II gene therapy for prevention of experimental vascular stenosis</td>
</tr>
<tr>
<td>2004</td>
<td>Gerald F. Dibona, MD</td>
<td>(1) Described the role of the renal nerves in control of renal function (renin secretion, sodium excretion, and renal blood flow); (2) demonstrated that increased neural activity to the kidneys limits their ability to excrete sodium</td>
</tr>
<tr>
<td>2005</td>
<td>John E. Hall, PhD</td>
<td>Defined the causative role of pressure-natriuresis in the development of hypertension</td>
</tr>
<tr>
<td>2006</td>
<td>M. Judah Folkman, MD</td>
<td>(1) Among the first to grow endothelial cells in vitro; (2) discovered the mechanism of angiogenesis that led to clinical trials of angiogenesis inhibitors; (3) described the use of silicone rubber implantable polymers for the sustained release of drugs</td>
</tr>
<tr>
<td>2007</td>
<td>Jorge H. Capdevila, PhD</td>
<td>(1) Demonstrated how hypercholesterolemia and atherosclerosis alter endothelium-dependent vasodilatation; (2) characterized NADPH oxidase as a source of radicals in hypertension; (3) discovered that the adaptive immune system plays a role in the genesis of experimental hypertension</td>
</tr>
<tr>
<td>2008</td>
<td>Kenneth E. Bernstein, MD</td>
<td>(1) Cloned the angiotensin-converting enzyme gene and demonstrated its tissue specific expressions and activities; (2) cloned the angiotensin II type 1 receptor</td>
</tr>
<tr>
<td>2009</td>
<td>Barry M. Brenner, MD</td>
<td>Demonstrated that inhibition of renin-angiotensin provides renal protection in hypertension, diabetes mellitus, and a variety of primary renal diseases</td>
</tr>
<tr>
<td>2010</td>
<td>William B. Campbell, PhD</td>
<td>(1) Described a role for endothelium-derived factors in the regulation of vasomotor function and aldosterone; (2) discovered a new class of endothelium-derived eicosanoids (epoxyeicosatetraenoic acids)</td>
</tr>
<tr>
<td>2011</td>
<td>Theodore W. Kurtz, MD</td>
<td>Identified molecular gene variants contributing to cardiovascular and metabolic phenotypes in experimental models of hypertension</td>
</tr>
<tr>
<td>2012</td>
<td>Friedrich C. Luft, MD</td>
<td>Seminal discoveries on the physiology of renal sodium handling in hypertension, the pathophysiology of hypertension-mediated target organ injury, and the genetics of hypertension</td>
</tr>
<tr>
<td>2013</td>
<td>Mordecai P. Blaustein, MD</td>
<td>Discovered and described physiological significance of plasma membrane sodium-calcium exchanger and endogenous ouabain</td>
</tr>
<tr>
<td>2014</td>
<td>John W. Funder, MD</td>
<td>(1) Characterized mineralocorticoid receptor in kidney and other tissues; (2) characterized blood pressure–independent effects of aldosterone to produce inflammation and fibrosis; (3) demonstrated role of 11 hydroxysteroid dehydrogenase in converting cortisol/corticosterone to inactive metabolites</td>
</tr>
<tr>
<td>2015</td>
<td>Juan Carlos Romero, MD</td>
<td>(1) Described interactions of prostaglandins with intrarenal renin-angiotensin system; (2) described roles of prostaglandins and NO in regulation of renal hemodynamics; (3) developed innovative approaches for imaging the kidney</td>
</tr>
<tr>
<td>2016</td>
<td>Carlos M. Ferrario, MD</td>
<td>(1) Determined mechanism of action of angiotensin in brain; (2) identified new pathways leading to formation of angiotensin (1-7); (3) described mechanism of action of angiotensin-converting enzyme and angiotensin receptor antagonists; (4) described the role of angiotensin II in pathogenesis of atherosclerosis</td>
</tr>
<tr>
<td>2017</td>
<td>Curt D. Sigmund, PhD</td>
<td>(1) Described molecular biology and genetics of renin-angiotensin; (2) helped to define the importance of renin-angiotensin in blood pressure regulation and hypertension; (3) described the regulation of vascular function and blood pressure by peroxisome proliferator-activated receptor-γ</td>
</tr>
</tbody>
</table>

(Continued)
provides an overview of the evolution of the understanding of the pathophysiology of hypertension and the application of this understanding to its treatment. Not surprisingly, perhaps reflecting the recommendations of the 1979 NHLBI Hypertension Task Force, several lines of discovery stand out, including the following: (1) neural, hormonal, renal, and vascular control of the circulation and arterial pressure; (2) identification of the components, relationships, and physiological effects of the renin-angiotensin-aldosterone system; (3) characterizations of the components and functional relationships of the sympathetic nervous system; (4) local regulation of vascular tone; (5) development of animal models to study genetic contributions and mechanisms of hypertension; (6) genetic contribution to human hypertension; and (7) delineation of the relationships of blood pressure and dyslipidemia with cardiovascular disease and stroke. Awards were also bestowed for the identification of secondary forms of hypertension and for early experiences with a nutritional intervention and with antihypertensive drug trials. A number of the more basic observations have catalyzed the development of different classes of antihypertensive drugs.

**Genetic Strategies**

Provoked by high heritability estimates and catalyzed by developing new technologies over the past 2 decades, including complete sequencing of the human genome in 2000 and the International HapMap Project in 2003, the search for genetic contributions to hypertension has been intense. The potential for developing new therapeutics and diagnostic tests to predict an individual’s response to antihypertensive therapy is one of the motivating forces in this search. Based on evolving technologies, several strategies have been used in the search for specific hypertension-related genes. Animal models (eg, selectively bred rats, congenic rat strains, and knockout mouse models) provide powerful approaches for evaluating genetic loci and genes associated with hypertension. Comparative mapping strategies allow for the identification of syntenic genomic regions between the rat and human genome.

In humans, specific genetic variants have been identified in rare mendelian forms of hypertension; however, these variants are not applicable to the majority of patients with essential hypertension. Two approaches have been used to identify genetic determinants of essential hypertension, linkage analyses and association studies. Strategies in the search for blood pressure–related genes have included the study of variants in rare mendelian forms of hypertension, the investigation of candidate genes or a previously identified genetic locus, and genome-wide scans. Genome-wide association studies have been facilitated by the availability of dense genotyping chips and the International HapMap (2005–2009).

Numerous genes have been studied, and genetic variants associated with essential hypertension have been identified. These include genes from the renin-angiotensin-aldosterone system, the epithelial sodium channel, the adrenergic receptor system, and α-adducin.

To date, although both candidate gene studies and genome-wide association studies have provided suggestive evidence of specific genetic contributions to blood pressure and/or hypertension, replication has been problematic. Progress has been hampered by the facts that hypertension is a polygenic disorder, different combinations of genes may influence blood pressure in a unique manner, and environmental factors affect the impact of genes on blood pressure. Future studies may move beyond DNA-based sequence approaches and involve the evaluation of heritable changes in gene expression.

**Translation Into Clinical Practice and Overall Impact**

Over the past several decades, there have been a number of federal initiatives to encourage translation of these scientific advances to the evaluation, treatment, and prevention of hypertension. In response to the convincing epidemiological evidence for the cardiovascular consequences of elevated blood pressure, a 1965 report of the US President’s Commission on Heart Disease, Cancer, and Stroke recommended a nationwide increase in screening and treatment of high blood pressure. However, in the absence of evidence of the benefits of lowering blood pressure, no action was taken at that time. This evidence was provided several years later by the Veterans Administration Cooperative Studies. Consequently, in 1972, the Secretary of Health, Education, and Welfare (Elliot Richardson) charged the Director of the National Heart and Lung Institute (Dr Theodore Cooper) to develop a national plan of action. Richardson was influenced by recommendations from Mary Lasker, a long-time supporter of biomedical research and lobbyist for improving the nation’s health (the Veterans Affairs Cooperative Study was supported in part by the Lasker Foundation) and Dr Michael DeBakey, a noted cardiovascular surgeon. The result was the establishment of the National High Blood Pressure Education Program (NHBPEP). The program was designed and implemented by the then US National Heart and Lung Institute to raise public awareness and stimulate blood pressure screening and treatment throughout the nation. The program evolved into a cooperative effort among professional and voluntary health agencies, state health departments, and community groups, coordinated by the NHLBI, with the overall goal to reduce death and disability related to high blood pressure through programs of professional, patient, and public educa-
tion. Dr Edward Roccella served as coordinator of the program for most of its existence.

Shortly after its creation, the NHBPEP established 4 task forces, with the following objectives: (1) task force I was created to develop definitions, standards of care, and effective treatment regimens; (2) task force II was created to develop a plan for education of health professionals; (3) task force III was created to develop a program of public education; and task force IV was created to study the impact of the projected program on the existing healthcare system and assess the resources needed for full implementation of the program. Membership on the task forces included nonfederal health professionals and representatives of several federal health agencies. Reports of the task forces were published in 1973. Reflecting information available at the time, task force I recommended the following78:

A subject with a diastolic pressure of 95 mm Hg or more and/or a systolic pressure of 160 mm Hg or more should be referred for a secondary screen. At the secondary screen, the diastolic pressure should be chosen as the sole basis for recommending disposition. It is recommended that a diastolic pressure of 105 mm Hg or more be treated; a diastolic pressure below 95 mm Hg be rescreened periodically; and individual recommendations be considered for intermediate pressures.

The NHBPEP also created the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC). The initial charge to the JNC was to provide practical recommendations for defining acceptable blood pressure levels and treatment strategies. These reports have been a critical component of the NHBPEP. The intent has been to “synthesize the available scientific evidence, and then to unify the positions of member organizations and send one clear message.”79a Each successive report has been updated based on new clinical evidence and the availability of new antihypertensive agents. The updated reports have recommended progressively more rigorous criteria for defining and treating hypertension. Table 6 lists the defining criteria in the latest JNC report (JNC VII), published in 2003.80 Although limited, increasing evidence suggests that home blood pressures and ambulatory blood pressure recordings predict target organ damage and morbidity events more reliably than do clinic measurements. Recent studies have attempted to identify the “normal” blood pressure ranges for these measurements.

Since inception of the NHBPEP, hypertension awareness, treatment, and control rates in the United States have improved (Table 7),80,81 and the age-adjusted mortality rates for stroke and coronary heart disease have declined by 57% and 63%, respectively, between 1979 and 2007 (Figure 6).82 It is likely that improved hypertension control has contributed to these favorable trends. In clinical trials of antihypertensive therapy, there has been a 35% to 40% reduction in stroke incidence, a 20% to 25% reduction of myocardial infarction, and a >50% reduction in the incidence of heart failure.83 It is likely that this remarkable success is at least partly the result of broad-based and diverse research programs supported by the federal government, pharmaceutical companies, professional societies, voluntary health agencies, and private foundations.

Table 6. Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure 7 Criteria for Defining Hypertension in Adults, Age ≥18 y

<table>
<thead>
<tr>
<th>Category</th>
<th>Systolic, mm Hg</th>
<th>Diastolic, mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;120</td>
<td>&lt;80</td>
</tr>
<tr>
<td>Prehypertension</td>
<td>120 to 139</td>
<td>0 or 80 to 89</td>
</tr>
<tr>
<td>Stage 1 hypertension</td>
<td>140 to 159</td>
<td>0 or 90 to 99</td>
</tr>
<tr>
<td>Stage 2 hypertension</td>
<td>≥160</td>
<td>0 or ≥100</td>
</tr>
</tbody>
</table>

Source is Reference 80.

Table 7. Trends in Hypertension Awareness, Treatment, and Control in US Adults

<table>
<thead>
<tr>
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<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Awareness</td>
<td>51%</td>
<td>73%</td>
<td>68%</td>
<td>69%</td>
<td>81%</td>
</tr>
<tr>
<td>Treatment</td>
<td>31%</td>
<td>55%</td>
<td>53%</td>
<td>58%</td>
<td>73%</td>
</tr>
<tr>
<td>Control</td>
<td>10%</td>
<td>29%</td>
<td>27%</td>
<td>31%</td>
<td>50%</td>
</tr>
</tbody>
</table>

Table is based on National Health and Nutrition Examination Survey data. Data derived from References 80 and 81.
Perspectives

Despite scientific advances over the past several decades and translation of these discoveries into the clinical arena, researchers, healthcare providers, and policy-makers should not be complacent about past successes. Hypertension remains a major contributor to the global burden of disease. The worldwide prevalence is ≈26%, totaling 1 billion people. Because a larger proportion of the world’s population is expected to be older in 2025, hypertension prevalence has been projected to increase to ≥29% by that time. Cardiovascular disease, including stroke, heart attack, and heart failure, is the leading cause of death and disability worldwide; elevated blood pressure accounts for 62% of stroke and 49% of coronary heart disease cases. Approximately 7.6 million deaths (≈13% to 15% of the total) and 92 million disability-adjusted life-years worldwide were attributable to high blood pressure in 2001. In the United States, hypertension prevalence remains high and hypertension control rates are unacceptably low. Currently, ≈73 million Americans have hypertension, and blood pressure is uncontrolled in 50%. Cardiovascular disease is the leading cause of mortality in the United States, accounting for ≈34% of all deaths annually. Building on the impact of the NHLBI Hypertension Task Force in the 1970s, this may be an appropriate time to convene a task force to recommend both future research directions and new strategies for the translation of scientific discoveries into the clinical arena.

Figure 6. Age-adjusted mortality rates for coronary heart disease and stroke in the United States, 1979–2007.82

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