

Review Paper

Historical Perspectives on the Management of Hypertension

Marvin Moser, MD

As late as the 1950s, elevated blood pressure was considered by many expert physicians to be necessary for the adequate perfusion of vital organs. Although the morbidity and mortality risks of hypertension were known at that time to insurance companies, which often refused life insurance policies to people with high blood pressure, there was a lag in the recognition of the dangers of hypertension in the medical community. Following the pioneering efforts of researchers who began to treat patients with malignant hypertension, the results of clinical trials and population studies, and the availability of effective antihypertensive agents, hypertension management improved rapidly. This review traces the history of hypertension management from the 1940s, when President Franklin Delano Roosevelt died of a cerebrovascular accident—a result of uncontrolled hypertension—to today, when a large number of patients, even those with less severe hypertension, are being treated successfully, with a resulting dramatic decrease in hypertension-related vascular disease. (J Clin Hypertens. 2006;8(8 suppl 2):15–20) ©2006 Le Jacq

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.—J.H. Hay, 1931

Hypertension may be an important compensatory mechanism which should not be tampered with, even were it certain that we could control it.—Paul Dudley White, 1937

From the Department of Internal Medicine,
Yale University School of Medicine, New Haven, CT
Address for correspondence:
Marvin Moser, MD, 13 Murray Hill Road,
Scarsdale, NY 10583
E-mail: moserbp@aol.com

It has been 70 years since the cardiologists J.H. Hay,¹ Paul Dudley White,² and others wrote that high blood pressure (BP) may be a natural and necessary compensatory phenomenon that should be left alone even if there were effective treatments. Large clinical trials and epidemiologic studies have subsequently proved otherwise; elevated BP is clearly a cardiovascular (CV) risk factor and we can now say with certainty that treating hypertension reduces CV morbidity and mortality. The history of the management of hypertension is an exciting story of a major, successful preventive medicine effort.

HYPERTENSION IN THE 1940s

Those of us who were house staff officers in the 1940s recall that every third or fourth medical bed was occupied by sick, middle-aged patients with some complication of hypertension—heart failure, stroke, accelerated hypertension, or renal failure.³ Yet in 1941, in the first edition of the “gold standard” pharmacologic textbook by Drs. Goodman and Gilman,⁴ only 10 references to hypertension or its therapy were included in a volume of more than 1300 pages. Among the antihypertensive agents listed were thiocyanates, barbiturates, bismuth, and bromides. Potassium thiocyanate was introduced in 1940 to treat hypertension but was relatively ineffective at the dosages used and had many potential side effects. Similarly, barbiturates, bismuth, and bromides were mainly supportive rather than therapeutic in nature and were used along with lifestyle measures—rest and avoidance of stress (both emotional and physical).⁵

The natural history of untreated hypertension is illustrated by the case of President Franklin Delano Roosevelt, who had a BP reading of 162/98 mm Hg in 1937 at the age of 54 but, consistent with medical knowledge and opinion at that time, did



www.lejacq.com

ID: 5836

not receive therapy to reduce his BP from his personal physician, Admiral Ross McIntire—an ear, nose, and throat specialist by training.^{6,7} By 1940, Roosevelt's BP had reached 180/88 mm Hg, and in 1941, a BP reading of 188/105 mm Hg was recorded.⁸ Phenobarbital and massages were prescribed.⁶ Later that year, and in 1943 and 1944, Roosevelt's failing health led to speculation in the press regarding his competence to continue in office.⁸ He had developed shortness of breath, orthopnea, lethargy, drowsiness, and other evidence of heart failure. McIntire continued to treat the president for recurrent bronchitis and sinusitis.⁶

In March 1944, cardiologist Howard G. Bruenn, a naval medical officer, examined Roosevelt at the request of Mr. Roosevelt's daughter. "I asked [Roosevelt] a lot of questions and there were a few things he mentioned very casually which suggested that he might be having some trouble," Bruenn said years later in an interview. "Then I went over his neck and chest and I was ... appalled at what I was finding—[evidence of] congestive heart failure."⁹ The president had pulmonary edema and an enlarged heart on chest x-ray, electrocardiographic signs of left ventricular hypertrophy, and proteinuria on urinalysis.⁶ That year, Kempner had reported the BP-lowering effects of a strict, low-salt rice diet consisting of rice boiled in distilled water and fruit juices¹⁰; so, in addition to reducing Roosevelt's alcohol and cigarette use and limiting his workday to 4 hours to allow for bedrest, Bruenn initiated digitalis therapy and tried a low-salt diet, with some improvement in heart failure symptoms. While there were some BP-lowering medications available, all of them had potentially severe side effects. In addition, although surgical procedures such as sympathectomy were being performed for severe hypertension, this was not considered in the president's case. BPs of 180–230/110–140 mm Hg were recorded in 1944, and 62-year-old Roosevelt suffered a series of CV accidents.⁶ At the time of Roosevelt's re-election in November 1944, his BP was 200/100 mm Hg. A few months later, before the Yalta Conference in February 1945, Roosevelt's BP was recorded as 260/150 mm Hg. The impact of Roosevelt's health on the Yalta negotiations remains a debatable subject; some historians have maintained that the president's lack of concentration and impaired memory due to his poor health may have prevented him from taking a stand against Stalin's desire to control major portions of Eastern Europe. Others, however, have commented that this approach was necessary to gain Russian involvement in the war with Japan.¹¹ Seeing Roosevelt at Yalta, Churchill's

physician Lord Moran noted that Roosevelt was "looking straight ahead with his mouth open as if he were not taking things in. To a doctor's eye, the President appears very ill. I'd give him no more than a few months to live."⁸

While sitting for an artist's portrait and signing papers at the "the Little White House" in Warm Springs, GA, on April 12, 1945, Roosevelt suddenly lost consciousness after complaining of a severe headache. Examining the patient 15 minutes later, Bruenn recorded the president's BP at >300/190 mm Hg. Roosevelt died at the "young" age of 63. No autopsy was performed. Bruenn certified the cause of death as a cerebral hemorrhage. Bruenn wrote later in the *Annals of Internal Medicine*, "I have often wondered what turn the subsequent course of history might have taken if the modern methods for the control of hypertension had been available."⁶

Roosevelt represents a textbook case of untreated hypertension progressing to target organ failure and death from stroke. In the 1940s, treatment of elevated BP was not deemed appropriate unless malignant or accelerated hypertension was present. As noted, ineffective and potentially harmful drug therapy or extensive surgery with a high rate of morbidity were the only treatment options; this approach may have seemed reasonable at that time only in severe cases. In the late 1940s, Dr. Charles Friedberg wrote in his textbook *Diseases of the Heart*,

In a patient with mild benign hypertension—[defined as a] blood pressure <200/<100 mm Hg, there is no indication for use of hypotensive drugs. Continued observation is desirable and conservative treatment consisting of reassurance, mild sedatives, and weight reduction is indicated.¹²

In the 1948 textbook *Cardiology*, Evans noted that

The blood pressure is [considered to be] raised when the systolic pressure is 180 or over, and/or the diastolic pressure is 110 or over, on three consecutive examinations, and in the presence of clinical, radiological and cardiographic evidence of cardiovascular hypertrophy.¹³

Some physicians recognized that the prognosis of patients with malignant hypertension was often a year or less.¹⁴ They began to experiment with methods of reducing BP. A low-salt diet had been suggested as early as 1922 by Allen and Sherrill¹⁵ as a way of reducing BP, but while their recommendations were adopted in Europe, they did not receive much attention in the United States. The 1944

Kempner rice diet included a daily intake of 2000 calories and consisted of rice, fruit, and juices that limited sodium intake to a total of 150 mg, protein to 20 g, and fat to 5 g. Lean meat and fish could be added only when BP was controlled.¹⁰ This regimen significantly reduced BP and the complications of malignant hypertension at least temporarily, with disappearance of papilledema and retinal hemorrhages, regression of cardiac hypertrophy, and improvement in heart and renal failure in some patients. Not everyone responded to the diet: in 1948, Kempner reported that out of 500 patients, BP fell in 322 of them while enrolled in the program.¹⁴ Not surprisingly, patients found it difficult to comply with the rice and fruit juice regimen. Sir George Pickering described it as “insipid, unappetizing, monotonous, unacceptable and intolerable,” saying that to stay on it “required the asceticism of a religious zealot.”¹⁶ It is notable that Kempner himself did not attribute the hypotensive effects of the diet to its low-sodium content but to other factors such as the low-protein content and enzymatic effects.¹⁷ The hypotensive effect of the diet was in fact shown by Grollman¹⁸ in 1945 to be due to its low-sodium content.

Other rather radical methods of reducing BP in patients with malignant or accelerated hypertension included injections of pyrogens such as typhoid bacilli and, as noted, radical surgical methods such as sympathectomy and later adrenalectomy (each of which necessitated 3–6 weeks of inpatient postoperative treatment).¹⁴ While surgical interruption of the sympathetic nervous system halted the progression of severe hypertension in as many as 50% of patients, it also carried significant side effects, namely severe orthostatic hypotension, as well as the not insignificant risks of surgery.¹⁴

One of the icons of antihypertensive therapy, the late Dr. Edward D. Freis, was one of the first to try the antimalarial agent pentaquine as a possible hypotensive agent in the treatment of malignant hypertension. During World War II, researchers working with malaria had noted that healthy volunteers treated with high doses of the drug developed orthostatic hypertension. Freis tried the drug in a desperate attempt to save the life of a patient with malignant hypertension who was turned down for sympathectomy as a poor surgical risk.¹⁹ Pentaquine reduced the patient’s diastolic BP from 160 to 100 mm Hg and relieved symptoms including headache and hematuria. “This was the first time we had seen reversal of the signs of malignant hypertension following an antihypertensive drug. It was an exciting experience,” Freis noted.¹⁴

In the 1940s, impressive hypotensive efficacy had been noted with the herb *veratrum viride*. While veratrum reduced BP and resulted in improvement of congestive heart failure, significant side effects, most notably severe nausea and vomiting, were noted. There was a narrow therapeutic to toxic range. Lower doses of veratrum, when used with a low-sodium diet, also resulted in BP lowering.

HYPERTENSION IN THE 1950s

The aim of science is not to open a door to endless wisdom, but to put a limit to endless error.
—Bertold Brecht, *The Life of Galileo*

In 1950, Dr. Tinsley R. Harrison²⁰ published the first edition of his *Principles of Internal Medicine*, which continued to advocate that the treatment of hypertension “should be based on symptoms of coronary difficulties. Those with chest pain or other overt signs of disease should have their hypertension treated; others should not.” Academicians of the early 1950s continued to believe that hypertension was not a disease until it caused symptoms. In a 1955 paper, Dr. George A. Perera²¹ of Columbia University noted that in a study of 300 patients with hypertension diagnosed at an average age of about 40 years, most of these patients did not experience significant organ changes for many years when compared with normotensives and did not die until their mid-50s. Perera commented that hypertension was relatively benign and that “one is forced to conclude that ... hypertension lasts longer than generally supposed” but also that the label of hypertension might be applied too readily; for example, it should not be applied “to patients of advanced years with blood pressures of 160/80 mm Hg to 200/110 mm Hg.”²²

For many years, the term *benign essential hypertension* was used. Despite evidence that we presented in the late 1950s on the clinical benefits of treating malignant hypertension, including electrocardiographic changes showing reversal of left ventricular hypertrophy, a group of physicians who have been referred to as the “New York Nihilists” refused to accept that treatment was helpful. “Benefit achieved in the management of malignant hypertension,” they stated, “may represent the ‘natural history of the disease.’”^{3,16}

The search continued for alternatives to sympathectomy. Phenoxbenzamine, a sympathetic nerve blocker, and the ganglion blockers hexamethonium, pentolinium, mecamylamine, and a peripheral adrenergic inhibitor (guanethidine) were discovered. They were all highly effective at reducing BP, but significant side effects and adherence to therapy were major problems.¹⁴ Reserpine, the active alkaloid in

rauwolfia serpentina, was initially used as a sedative but, beginning in the 1950s, it was also shown to be effective in lowering BP through a central action and reducing circulating catecholamines.⁵ Rauwolfia preparations were also poorly tolerated at the dosages that we were using to treat patients, and fatigue, insomnia, and depression were not uncommon.²³ Hydralazine, a vasodilator, was also in use as an antihypertensive agent by the late 1950s but, while it also effectively reduced BP, tolerance and side effects such as headaches and tachycardia often were noted. In an attempt to reduce the incidence of side effects, combinations of agents in low doses were tried. A combination of hydralazine and hexamethonium, or rauwolfia and pentolinium, or a combination of all three agents were all used, but side effects remained a problem.²³

In the fall of 1957, clinical trials began on a drug that at first did not hold promise as a major antihypertensive agent. None of us studying this medication, including Freis in Washington, DC, and Harriet Dunstan in Cleveland, OH, knew that this drug—chlorothiazide—would prove to be an important breakthrough in the pharmacologic management of hypertension.²⁴ Thiazide diuretics were effective orally and were more acceptable and convenient than daily injections of diuresis-causing mercury and BP was reduced as effectively as with a rigid, low-salt diet. At first we used diuretics as adjunct therapy, as our first paper on diuretic use in hypertensives indicated.²⁵ Later on, we also found them to be effective as monotherapy.²⁶ In large trials, they reduced morbidity and mortality associated with hypertension.²⁷ The thiazide diuretics effectively reduced BP, were well tolerated, and clearly prolonged life in hypertensive patients.

As therapy became easier and more effective, more people with less severe hypertension could now be treated. The benefit/risk equation had now shifted to the benefit side. The effectiveness of diuretics in the 1950s is illustrated by one of the cases we followed. In 1953, a 42-year-old man was found to have a BP of 250/150 mm Hg on an insurance physical.¹⁶ He was asymptomatic at the initial examination but had evidence of left ventricular hypertrophy. He was started on multiple agents, including rauwolfia and hydralazine, but his BP remained above 150/100 mm Hg until we added chlorothiazide to his regimen in 1959; his BP decreased to 120/80 mm Hg and his electrocardiogram normalized. He lived for 25 years to the age of 67, when he died suddenly in 1978 while chopping wood. Had effective therapy not been available, his prognosis would have been less than

2 years' life expectancy in a man of 42 years with severe hypertension and evidence of target organ involvement. Thiazide diuretics continue to be used as initial agents in the management of hypertension or as a necessary component in a multidrug regimen. Despite efforts to minimize the benefits and maximize the potential problems with diuretics, major clinical trials have reported a decrease in morbidity and mortality with their use.²⁸ The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)²⁹ results confirm the benefits of these medications.

As the search for effective pharmacotherapy for hypertension continued, the exploration of the underlying causes of elevated BP also progressed. In 1957, Page³⁰ published his mosaic theory of hypertension, advancing the idea that the mechanisms underlying hypertension are multiple, involving several regulatory systems including the heart and vasculature, the kidneys, liver and the endocrine and nervous systems. Page's theory is still of interest today, as it may help to explain why individual patients respond well to certain antihypertensive therapies and not to others.

HYPERTENSION IN THE 1960s TO THE 1990s

Debates among clinicians regarding the benefits of antihypertensive therapy continued into the 1960s and 1970s, even following the results of the first Veterans Administration Study³¹ in severe hypertensives, published in 1967. This study utilized a combination of a diuretic, reserpine, and hydralazine to control BP in severe hypertensive patients. The trial demonstrated that antihypertensive drug treatment reduced the incidence of stroke, congestive heart failure, and kidney damage in patients with diastolic BPs >105 mm Hg.

In the 1960s, the Framingham Heart Study,³² a longitudinal study begun in 1949, reported a strong correlation between elevated BP and heart attacks, congestive heart failure, stroke, and kidney damage. Based on epidemiologic and treatment data, the National High Blood Pressure Education Program was started in 1972, with the goal of enlightening health care professionals and the public on the dangers of hypertension and the lifesaving benefits of treatment.^{14,33}

The early 1960s also witnessed the next significant step in pharmacologic discoveries for hypertension management. Propranolol was the first β blocker introduced into clinical practice, followed later by agents with increased cardioselectivity. The mechanism by which β blockers reduce BP continues to be debated. These agents reduce heart rate,

cardiac output, and renin levels, but also have an effect on baroreceptor setting and a direct action on the central nervous system.⁵ The β -blocker class is heterogeneous, with the most recently discovered agents having vasodilatory effects, either through α -blockade or by stimulation of the L-arginine/nitric oxide (NO) pathway.³⁴ Since impaired NO bioavailability and endothelial dysfunction are associated with arterial stiffness, there is some rationale for the hypothesis that vasodilating β blockers may have a greater effect than earlier agents such as atenolol on reducing central aortic pressure.

But even with progress in research and treatment in the 1960s, there were still skeptics. As late as 1966, Friedberg³⁵—who had noted that treating anyone with BP <200/100 mm Hg was not indicated—now stated that, “Many of the symptoms of patients with hypertension are regarded as psychoneurotic,” and there is a “psychopathologic personality ... associated with hypertension.” It was still the belief of many experts that hypertension was a natural process of aging (and that a systolic BP of “age + 100” was a normal level).

The next milestone in the story of hypertension treatment occurred in 1977, with the publication of the first report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC).³⁶ The Committee, which I was honored to chair, was appointed by the National Heart, Lung, and Blood Institute and composed of representatives from most of the major medical organizations. The first JNC report suggested that if BP was $\geq 160/95$ mm Hg, it should be rechecked in 1 month in all persons.³³ In people 50 years and younger with BPs of 140/90 mm Hg to 160/95 mm Hg, BP should be checked every 2 to 3 months, while people older than 50 years with a BP level in this range should be checked within 6 to 9 months. No specific action was necessary unless the diastolic BP was ≥ 105 mm Hg.³³ The emphasis in JNC I was on treating the diastolic pressure; there were no recommendations for the staging of hypertension based on systolic pressure.

Since 1977, with the availability of more data from large clinical trials, the recommendations of the JNC reports have become increasingly aggressive and specific, with emphasis shifting more to the treatment of systolic pressures, especially in people older than 55–60 years. One of the highlights of the most recent report, JNC 7, was the introduction of the term *prehypertension* to stress lifestyle changes and regular monitoring in individuals with BPs previously considered normal or high-normal, i.e., 120–129/80–89 mm Hg.

Lifestyle interventions should be initial treatment in these individuals, but pharmacotherapy may be considered.^{37,38} It is interesting to note that at the time of JNC I, there were fewer than 30 drugs available for the management of hypertension; at the time of JNC 7 in 2003, there were more than 100.³³ The availability of excellent, effective, and relatively safe medications—such as calcium channel blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers in addition to diuretics and β blockers—has made it possible to reduce BP to goal levels in more than 50% of patients. Two or more agents are usually necessary. Lowering BP with one or a combination of medications has been shown to reduce CV events.

HYPERTENSION IN THE 21ST CENTURY

A little fire is quickly trodden out; which, being suffered, rivers cannot quench.—William Shakespeare, Henry VI

Treat elevated BP early and organ damage is minimized or prevented. Wait until there is clinical evidence of vascular disease and, while benefit is still noted, results may not be as good as with early intervention. While we continue to redefine our approach to treatment, we no longer wait to act until BP is $>200/100$ mm Hg and the patient has evidence of heart, brain, or kidney disease. We have effective, well tolerated pharmacologic therapies, the use of which has resulted in a dramatic decrease in CV events. Clinical trial evidence is convincing that patients with stage 1 hypertension (BP 140/90 mm Hg to 160/100 mm Hg) will benefit from therapy.³⁷ There is very preliminary evidence that suggests hypertension may be delayed, or possibly even prevented, with early and appropriate therapy in patients with prehypertension.³⁹ Like fire, we now know that hypertension is best stopped early and aggressively or, better yet, prevented.

The modern management of hypertension represents a major success story in preventive medicine.⁴⁰ Almost every large clinical trial has shown that the lower the BP, the better the outcome, regardless of how it is achieved.⁴¹ But there are still challenges. How do we increase the number of hypertensive patients who are controlled at goal BPs of $<140/90$ mm Hg? How should hypertension be defined? When should pharmacologic therapy be added to lifestyle recommendations? What is the best pharmacologic strategy for a given patient? Given the potentially huge impact of treating more patients with elevated BP and reducing morbidity and mortality rates still further, it is interesting to note that hypertension is not a popular media topic, like cancer or the flu.

And despite the high prevalence of hypertension in our population, there are no telethons or walkathons to fund BP research. But progress in treating hypertension has been remarkable since the days when a monthly digest magazine proclaimed in 1949, "High Blood Pressure? Don't be alarmed—when the facts become known, a brooding and paralyzing fear should lift from the land."¹⁴

REFERENCES

- Hay JH. The significance of a raised blood pressure. *BMJ*. 1931;2:43–47.
- White PD. *Heart Disease*. 2nd ed. New York, NY: MacMillan Co; 1937:326.
- Moser M. *Myths, Misconceptions and Heroics—The Story of the Treatment of Hypertension from the 1930s*. 2nd ed. Darien, CT: Le Jacq Communications, Inc; 2002.
- Goodman L, Gilman A. *The Pharmacological Basis of Therapeutics*. New York, NY: MacMillan Co; 1941.
- Rosenthal T. Contemplating the history of drug therapy for hypertension. *Blood Press*. 2004;13:262–271.
- Bruenn HG. Clinical notes on the illness and death of President Franklin D. Roosevelt. *Ann Intern Med*. 1970;72:579–591.
- Messerli FH. This day 50 years ago. *N Engl J Med*. 1995;332:1038–1039.
- Salerian AJ, Salerian GH. A review of FDR's mental capacity during his fourth term and its impact on history. *The Forensic Examiner*. Spring 2005;31–38.
- The Presidents. Franklin Delano Roosevelt, 32nd President [transcript]. "American Experience." WGBH television. 1994. Available at: http://www.pbs.org/wgbh/amex/presidents/32_f_roosevelt/filmmore/filmscript.html. Accessed May 26, 2006.
- Kempner W. Treatment of kidney disease and hypertensive vascular disease with rice diet. *N C Med J*. 1944;5:125–127.
- Herman A. Under Yalta's shadow: the forgotten legacy. *National Review Online*. February 11, 2005. Available at: <http://www.nationalreview.com/comment/herman200502110737.asp>. Accessed June 19, 2006.
- Friedberg CK. *Diseases of the Heart*. Philadelphia, PA: WB Saunders Co; 1949.
- Evans W. Hypertension. In: *Cardiology*. London, England: Paul B. Hoeber, Inc; 1948:204.
- Moser M. Evolution of the treatment of hypertension from the 1940s to JNC V. *Am J Hypertens*. 1997;10:2S–8S.
- Allen FM, Sherrill JW. Treatment of arterial hypertension. *J Metab Res*. 1922;2:429–545.
- Moser M. *Clinical Management of Hypertension*. 7th ed. Caddo, OK: Professional Communications, Inc; 2004.
- Ventura HO, Mehra MR, Messerli FH. Desperate diseases, desperate measures: tackling malignant hypertension in the 1950s. *Am Heart J*. 2001;142:197–203.
- Grollman A. Sodium restriction in diet for hypertension. *JAMA*. 1945;129:533–537.
- National Library of Medicine. Profiles in science. The Edward D. Freis papers: early career and work with anti-hypertensive drugs, 1940–1949. Available at: <http://profiles.nlm.nih.gov/XF/Views/Exhibit/narrative/drugs.html>. Accessed May 26, 2006.
- Harrison TR, ed. *Principles of Internal Medicine*. New York, NY: Blakiston Division; 1950.
- Perera GA. Hypertensive vascular disease: description and natural history. *J Chronic Dis*. 1955;1:33–42.
- Perera GA. *Hypertension*. In: Bell ET, ed. *Hypertension*. Minneapolis, MN: Minnesota Press; 1957.
- Moser M, Mattingly TW. Critical evaluation of drug therapy of hypertension. *Postgrad Med*. 1955;17:351–361.
- Black HR. Hypertension icons: interview with Marvin Moser, MD. *J Clin Hypertens (Greenwich)*. 2005;7:40–45.
- Moser M, Macaulay AI. Chlorothiazide as an adjunct in the treatment of essential hypertension. *Am J Cardiol*. 1959;3:214–219.
- Moser M. A decade of progress in the management of hypertension. *Hypertension*. 1983;5:808–813.
- Moser M, Herbert P. Prevention of disease progression, left ventricular hypertrophy and congestive heart failure in hypertension treatment trials. *J Am Coll Cardiol*. 1996;27:1214–1218.
- Moser M. Current hypertension management: separating fact from fiction. *Cleve Clin J Med*. 1993;60:27–37.
- ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs. diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA*. 2002;288:2981–2997.
- Page IH. The renin angiotensin pressor system. In: Bell ET, ed. *Hypertension*. Minneapolis, MN: Minnesota Press; 1957:66.
- Effects of treatment on morbidity in hypertension. Results in patients with diastolic blood pressures averaging 115 through 129 mm Hg. *JAMA*. 1967;202:1028–1034.
- Kannel WB, Schwartz MJ, McNamara PM. Blood pressure and risk of coronary heart disease: the Framingham study. *Dis Chest*. 1969;56:43–52.
- Moser M. From JNC I to JNC 7—what have we learned? *Prog Cardiovasc Dis*. 2006;48:303–315.
- Weber MA. The role of the new beta-blockers in treating cardiovascular disease. *Am J Hypertens*. 2005;18:169S–176S.
- Friedberg CK. *Diseases of the Heart*. Philadelphia, PA: WB Saunders Co; 1966.
- Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. A cooperative study. *JAMA*. 1977;237:255–261.
- The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA*. 2003;289:2560–2572.
- Moser M. Are lifestyle interventions in the management of hypertension effective? How long should you wait before starting specific medical therapy? An ongoing debate. *J Clin Hypertens (Greenwich)*. 2005;7:324–326.
- Julius S, Nesbitt SD, Egan BM, et al., for the Trial of Preventing Hypertension (TROPHY) Study Investigators. Feasibility of treating prehypertension with an angiotensin-receptor blocker. *N Engl J Med*. 2006;354:1685–1697.
- Moser M. Hypertension treatment—a success story. *J Clin Hypertens (Greenwich)*. 2006;8:313–314.
- Post W, Moser M, Kaplan N. A conversation with Drs. Kaplan and Moser about conflicting data, confusing results, and some recent treatment recommendations for the management of hypertension. *J Clin Hypertens (Greenwich)*. 2005;7:606–611.