

## Seven Decades of Progress

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On February 14th, Valentine's Day, the Public Broadcasting System (PBS) aired a special 2-hour program on heart disease, *The Hidden Epidemic: Heart Disease in America* ([www.pbs.org/wgbh/takeonestep/](http://www.pbs.org/wgbh/takeonestep/)). The program was a professional documentary that was superbly directed and produced.

The next day, one of the principal participants noted that he had been afraid to go to sleep after the program, afraid that he might not wake up in the morning. The message had been one of gloom and doom.

The report initially focused on the Framingham Heart Study,<sup>1</sup> which, along with other trials began in the 1940s and 1950s, helped to define the specific risk factors that result in cardiovascular morbidity and mortality. These findings have been of critical importance in directing physician practices to prevent cerebrovascular and coronary heart disease. The documentary carefully reviewed the facts that elevated blood pressure, abnormal lipid levels, and smoking increase the risk of cardiovascular events. It reviewed specific details of this ongoing landmark epidemiologic study with comments from Dr Dan Levy, the Director of the Framingham Project; Dr William Kannel, one of the original directors of the study; and Dr William Castelli, who also directed this project for several years. The Framingham study report was well done.

The program included pictures of plaque formation in the coronary arteries, and throughout this 2-hour program we were constantly reminded that no one was free of the potential for sudden death and that heart disease was a killer. Undoubtedly, heart disease results in more deaths than do other diseases and that people should do whatever they can to prevent it, but the program was downbeat

in that it overstressed the problems rather than the good news.

For example, little attention was paid to the major advances in the treatment of high blood pressure that have greatly contributed to the reduction in stroke and stroke death rates by more than 60% over the past 7 decades. There was little emphasis on the fact that the occurrence of heart failure has been reduced by more than 50% over the past 7 decades as a result of lifestyle changes and effective treatment of hypertension and other risk factors or that the incidence of heart attack had been reduced by more than 50% as a result of modification of the risk factors that were so carefully outlined.<sup>2</sup> Instead, surgical intervention was emphasized and the long waiting periods for cardiac transplantation were described for people with severe coronary disease who had not been treated effectively or even for those who have had stents or bypass surgery.

It is understandable for the media to exaggerate to make a point. Perhaps the National High Blood Pressure Education Program was guilty of the same process when it labeled hypertension "the silent killer" and graphically described a person with high blood pressure as having a ticking time bomb in his chest. It is perhaps understandable to exaggerate the importance of the prevalence of a disease process to get the attention of the public or government spending agencies, but it is a disservice to the public to ignore positive or optimistic aspects of a problem. Treatment of risk factors, especially hypertension and dyslipidemia, has significantly reduced coronary heart disease events, stroke, heart failure, and progression of kidney disease.

A portion of the February 14 program was devoted to the management of abnormal lipid levels with an extensive discussion on the effect of various treatments, primarily statins, on lowering



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cholesterol and low-density lipoprotein (LDL) levels. There were comments about lowering LDL cholesterol levels and possibly reducing plaque formation, but only passing mentions of the major changes in outlook for the patient at risk.

### THE HYPERTENSION STORY

It is of interest to look back 7 decades, when Paul White, an eminent cardiologist from Boston, claimed that elevated blood pressure was necessary in older people to perfuse the brain and kidneys and that people with hypertension should be left alone even if there were effective treatments.<sup>3</sup> It is also interesting to quote from Charles Friedberg's classic book *Diseases of the Heart*, written in the 1940s, in which he stated that "People with 'mild benign' hypertension, defined as blood pressures up to levels of 210/100 mm Hg, need not be treated and that there was no indication for hypertensive drugs," that "Many of the symptoms of patients with hypertension are regarded as psychoneurotic," and there is a "psychopathologic personality... associated with hypertension."<sup>4</sup> In addition, Dr George Perera, from Columbia-Presbyterian Medical School, claimed that hypertension was benign and that people actually lived for 10 to 12 years after they developed high blood pressure.<sup>5</sup> It was indeed benign if you believe that experiencing cardiovascular events at ages 50 to 55 is acceptable. It is remarkable to look back and see how far we have progressed in our understanding of and approach to the management of hypertension.

It is also of interest to note that the standard pharmacologic textbook, *The Pharmacological Basis of Therapeutics*, a 1300-page book written by Goodman and Gilman in 1941, had only 10 references to hypertension or its treatment.<sup>6</sup> In the 1940s, there were no effective treatments for hypertension other than extensive sympathectomies, possibly adrenalectomies, rigid low-sodium diets containing <150 mg/d of sodium and medications such as bismuth, bromides, and barbiturates.<sup>7</sup>

As recently as 1948, in his textbook *Cardiology*, Evans noted that "The blood pressure is (considered to be) raised only when the systolic pressure is 180 [mm Hg] or over, and/or the diastolic pressure is 110 [mm Hg] or over, on three consecutive examinations, and in the presence of clinical, radiological and cardiographic evidence of cardiovascular hypertrophy."<sup>8</sup>

Franklin Roosevelt represents a person with a textbook case of untreated hypertension that progressed to higher and higher blood pressures and eventually target organ failure and death from

a stroke in 1945 at the young age of 63.<sup>9</sup> He had all of the risk factors for early death; at that time the picture was gloomy. In the 1940s, treatment of elevated blood pressure was not deemed appropriate, even by people who were convinced that it was related to cardiovascular disease, unless malignant or accelerated hypertension was present. As noted, only moderately effective and potentially harmful drug therapy or extensive surgery with a high rate of morbidity were the treatment options. These approaches may have seemed reasonable at that time, but only in severe cases.<sup>10</sup>

Malignant hypertension, which is a rarity today because of early treatment of elevated blood pressure, was indeed a killer. The prognosis of people with this syndrome was 6 to 12 months. It was more malignant than most neoplasms. Yet, even in the 1950s, when some of us were treating this syndrome—lowering blood pressure and reversing heart failure, fundoscopic changes, and symptoms—some of the leading physicians of the time were in denial. "Reversal of left ventricular hypertrophy and signs of malignant hypertension were considered as part of the natural history of the disease"—despite the evidence.<sup>7</sup>

Over the past 6 or 7 decades, we have witnessed a dramatic change in the treatment of several of the major risk factors defined so clearly by the Framingham investigators and highlighted in the recent PBS broadcast. We have progressed from the time when Irvine Page and Ed Freis, pioneers in the management of hypertension, were injecting vasodilating pyrogens such as typhoid bacilli or anti-malarial medications to lower blood pressure.<sup>11,12</sup> In severe cases, the benefit of therapy appeared to outweigh the risks. Some people with accelerated or malignant hypertension showed improvement. Drugs such as reserpine, a central-acting medication that was effective in lowering blood pressure but produced depression; the veratrum drugs, which lowered blood pressure but had a narrow toxic-therapeutic range and induced nausea and vomiting; and hydralazine, a potent vasodilator, were also being used. Blood pressure was being lowered, but with considerable inconvenience to the patient who often could not tolerate therapy.<sup>13</sup>

In an attempt to reduce the incidence of side effects, combinations of agents in low doses were tried. A combination of hydralazine and hexamethonium, a ganglion-blocking agent; or rauwolfia and pentolinium (another ganglion blocker); or a combination of hydralazine, rauwolfia, and a ganglion-blocking agent were used, but side effects remained a problem.

We have progressed from the time when we were using ganglion-blocking agents or phenoxybenzamine, which produced a chemical sympathectomy but untoward symptoms like syncope and bladder or intestinal atony, to the present where effective and relatively safe drugs are now available. Yes, it is necessary to tell the public about risks, but it is equally important to emphasize progress.

In 1950, Dr Tinsley R. Harrison 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.”<sup>14</sup>

In the fall of 1957, clinical trials began on a drug that at first did not hold promise as a major anti-hypertensive agent. None of us studying this medication, including Freis in Washington, DC, and Harriet Dustan in Cleveland, knew that this drug, chlorothiazide, would prove to be an important breakthrough in the pharmacologic management of hypertension. Thiazide diuretics were effective orally and more acceptable and convenient to use than daily injections of diuresis-causing mercury; blood pressure was reduced as effectively as with a rigid, low-salt diet. At first, we used diuretics as adjunct therapy.<sup>15</sup> Later on, they were found to be effective as monotherapy. In large trials, the use of diuretics either as monotherapy or in combination with other newly introduced medications reduced morbidity and mortality rates associated with hypertension.<sup>16</sup> These agents were well tolerated, and their use clearly prolonged life in hypertensive patients. As therapy became easier and more effective, more people with less severe hypertension could be treated. The benefit-risk equation had clearly shifted to the benefit side.

In the 1960s and 1970s, the original Veterans Administration Studies proved that morbidity and mortality could be reduced by appropriate therapy, not just in patients with accelerated hypertension but in those with less severe disease.

In 1972, the National High Blood Pressure Education Program of the National Heart, Lung, and Blood Institute (NHLBI) was started.<sup>17</sup> This major program has periodically issued guidelines for the diagnostic and therapeutic evaluation of hypertension to improve awareness, detection, and treatment of high blood pressure. Since 1977, with the availability of newer effective medications and data from large clinical trials, which clearly demonstrated the benefits of lowering blood pressure, the recommendations of the Joint National

Committees on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC) have become increasingly aggressive and specific, with emphasis shifting more to the treatment of systolic pressures, especially in people older than 55 to 60 years.<sup>18</sup> It is interesting to note that at the time of the first JNC report,<sup>19</sup> there were fewer than 30 drugs available for the management of hypertension; in 2003, at the time of JNC 7,<sup>20</sup> there were more than 100. 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  $\beta$ -blockers—has made it possible to reduce blood pressure to goal levels in more than 50% of patients; 2 or more agents are usually necessary.

The NHLBI program has been successful in helping to increase the number of patients under treatment and to reduce morbidity and mortality from heart disease. I do not remember this program even being mentioned in the PBS special on heart disease: it may have been in passing. The numerous clinical trials that have demonstrated that the reduction in blood pressure dramatically reduces the occurrence of stroke, heart attack, heart failure, and progression of renal disease were only briefly alluded to on Valentine’s Day.

It is now also possible to reduce cholesterol and LDL levels to optimal levels in a large percentage of patients with available therapy and low-fat diets.

### THE CHOLESTEROL STORY

The cholesterol story is also a dramatic one. In the 1940s, only a few physicians, such as William Dock, were paying any attention to the management of dyslipidemia. Awareness of its importance awaited further data from epidemiologic studies. But Dock insisted that all of his residents eat tuna fish and drink tea at lunchtime. He had recognized the composition of plaque and was working on doing something about it.<sup>21</sup> Additional data clearly established a relationship between dyslipidemia and heart disease, and many newer treatment options were developed, including bile acid salts, niacin, fibrates, and finally statins. As data accumulated, definitions of “high risk” changed, as they had for blood pressure. Cholesterol levels up to 300 mg/dL and LDL levels of 160 mg/dL, once considered within normal limits for people without coronary heart disease, were now considered high; goal levels were reset at <130 mg/dL for LDL and <240 mg/dL for cholesterol. This shift in the benefit-risk ratio occurred as the well-tolerated statins

became available. There has been a remarkable reduction in cardiovascular events as a result of these interventions. Plaques have been stabilized or reduced, and therefore more people can go to sleep at night without fear.

No, we have not achieved a satisfactory reduction in blood pressure in as great a number of patients as we should. No, we have not achieved the lowering of cholesterol levels or correcting of dyslipidemia in as many people as we can. No, we have not convinced everyone who drinks too much to moderate alcohol intake or people who are obese and sedentary to change their habits as much as we should. But success in reducing cardiovascular events over the past 7 decades has been achieved; it is a mistake to ignore these optimistic facts.<sup>22</sup> It is a mistake to frighten the public with the specter of plaque formation or the potential of sudden death, which, as noted, was repeatedly highlighted on the PBS special, without presentation of positive data on heart disease prevention.

It is important to inform the public. It is equally important to correctly inform them that while there is a risk from the factors identified in the Framingham study, the risk can be dramatically reduced and in many cases reversed by appropriate therapy. Seven decades have passed since the 1940s, when only a few physicians recognized that elevated blood pressure and abnormal lipid levels were risk factors and that lowering blood pressure or correcting dyslipidemia would be beneficial. The stories of high blood pressure treatment and the management of lipid disorders are two of the most dramatic success stories of preventive medicine in our history. Along with the remarkable effects of vaccines for measles, mumps, and polio, and eradication of diseases such as typhoid fever, these efforts stand out as major achievements.

Yes, a heart attack is a serious event; yes, bypass surgery and stents save and prolong life; yes, patients are grateful when they receive excellent care *after* a stroke. Rousing enthusiasm for prevention is a difficult undertaking. People are grateful for care in a crisis but have far less appreciation for prevention of a stroke or heart attack that has never occurred. The message is a difficult one. There are few headlines about prevention, but when a new stent is introduced or a new cardiac transplant procedure described, the media responds. More optimistic broadcasts and emphasis on preventing disease are needed.

The next decade should be spent on improving approaches to persons with risk factors as

identified by Framingham and other studies, meanwhile recognizing that we have come a long way in managing these factors. The past 7 decades have been those of progress, not failure or stagnation. Programs presented in the PBS special may be counterproductive. Although some still believe that the public has to be frightened to act, it is equally if not more important to present facts that are encouraging.

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