CHAPTER 164

Historical Development of Antihypertensive Treatment

Edward D. Freis

Arterial blood pressure (BP) was not measured clinically until this century. However, the hardness of the arterial pulse has been the subject of considerable medical attention, including treatment, since ancient times. The early history related to hypertension has been collected by Ruskin in his important treatise, *Classics in Arterial Hypertension* (1), and I am indebted to him for much of the following discussion of that period.

As early as 2600 B.C. the *Yellow Emperor's Classic of Internal Medicine* (2) stated, "Nothing surpasses the examination of the pulse, for with it errors cannot be committed. In order to examine whether Yin or Yang predominates, one must distinguish a gentle pulse and one of low tension from a hard and bounding pulse. The heart influences the force and fills the pulse with blood." With remarkable insight the author states, "If too much salt is used in food, the pulse hardens." Also, he indicated the relationship between hypertension and congestive heart failure by stating that, "When the pulse is abundant but tense and hard like a cord there are dropsical swellings."

In the *Pulse Classic of Wang,* published in 280 A.D., some prognostic guidelines are given such as, "In cases of apoplexy, the pulse should be superficial and slow; if it is firm, rapid and large there is danger. Where there is pulmonary congestion a wiry and large pulse is favorable; but few can recover quickly if it is small and thready" (1). A medical text from the Ashurbanipal Library at Nineveh (669–626 B.C.) recommended venesection (which reduces BP) and cupping for the treatment of apoplexy. Leeches were used for apoplexy throughout the ancient world. Some ancient Chinese texts advised acupuncture or venesection when the pulse hardens (1).

The Romans also were much concerned with the pulse. The Roman patrician Cornelius Celsus (3) pointed out the increased rate and tenseness of the pulse with exercise, passion, and even the doctor's arrival! The latter is reminiscent of what we call today the "white-coat" phenomenon.

Lack of temperance in eating, and in emotions were regarded as injurious by ancient Chinese. The Arabic text Al-Azkhora (The Therapy) (1) was even more explicit in stating that "Nothing is more harmful to an aged person than to have a clever cook and a beautiful concubine." Hippocrates also said that sudden death is more common in the fat than in the lean (4).

E. D. Freis: Hypertensive Research Unit, Department of Veterans Affairs Medical Center, Washington, D.C. 20422.

Galen (131–201 A.D.) was greatly revered until the eighteenth century. Yet he probably held back medical progress at least in some areas. For example, he claimed that the pulse in apoplexy was weak and denied that the plethoric pulse syndrome described by Erasistrates was associated with stroke (5). By failing to associate increased arterial tension with apoplexy, Galen may have delayed the understanding of their relationship for many years.

On the other hand, Hippocrates (4) believed that paralysis was caused by apoplexy, which in turn, resulted from plethora of the brain. From examining head wounds, he made the important observation that the paralysis occurs on the side opposite the lesion. Venesection, which could reduce the arterial blood pressure, was recommended by the Hippocratic school to relieve cerebral plethora. This method continued as the major treatment for stroke into the eighteenth century.

The ancient Greeks and Romans treated apoplexy as an independent disease entity and did not realize its frequent connection with high blood pressure, then known as hardening of the pulse. For the treatment of paralysis, Soravas of Ephesus (120 A.D.) recommended cupping of the spine to draw the animals spirits down and out (1). He also recommended bleeding and emetics. If the patient was able to survive all this, he probably would make a good recovery.

For many centuries there had been bans on doing autopsies. These bans were lifted (at least in Basel, Switzerland) in the seventeenth century, when J. J. Wepfer in 1658 reported four individuals who had died of apoplexy (6). In each case he found a cerebral hemorrhage on the side opposite to the paralysis.

GROWTH OF KNOWLEDGE IN THE NINETEENTH CENTURY

Thomas Young (7) is known for his 1808 Croonian Lecture on the functions of the heart and arteries. Young was a man of universal interests and accomplishments. He mastered seven languages; he developed theories of light (Young-Huygens wave theory) and accommodation (lens curvature, color vision, astigmatism), and even carried out a partial translation of the Rosetta stone! These were only a part of his many diverse accomplishments.

In his studies of the circulation, he found "that the pressure of the blood at the beginning of the great trunk of the aorta is kept up without noticeable loss down to the branches of the lower order." The statement is essentially correct. He claimed to have measured the percent fall in systolic and diastolic blood pressure in dogs from the aorta to mesenteric arteries of 200-μm diameter. The decrement averaged 16 mm Hg. Approximately 150

years later, we remeasured the pressure drop using modern dynamic equipment (8) and found an average pressure drop of 17% systolic and 12% diastolic from aorta to mesenteric arteries of 200-μm diameter—a remarkable agreement, considering the methods used in Young's time. Young also affirmed the dependence of the quality of the arterial pulsation upon the force of the heart.

One of the best known contributors to the history of hypertension is Richard Bright (9), although there were others who preceded him in some aspects of his work. In the sixth century A.D., Aetios described sclerosis of the kidneys with possible manifestations of oliguria, hematuria, and dropsy in the absence of pain. Albuminuria was first noted by Cotugo in 1770 (1). In 1761, Morgagni found enlargement of the heart in autopsies exhibiting extensive hardening of the arteries (1).

Bright's principal contribution was to bring these various observations together, such as albuminuria, fullness and hardness of the pulse, and dropsy with inflammation or hardening of the kidneys. These were presented in well-described case histories illustrated by excellent color illustrations. In 1836 he expanded his observations to include apoplexy, serositis, hypertrophy of the left ventricle, and diminution of the specific gravity and urea content of the urine with increase in blood urea. He listed scarlatina or some other acute disease as the cause of this condition. Because of these accurate observations, Bright's disease and glomerulonephritis became synonymous. Bright also provided an accurate pathological description of glomerulonephritis and probably of nephrosclerosis as well. With respect to the latter, he noted the thickening of the arterioles not only in the kidneys but also throughout the body.

In 1872, Gull and Sutton (10) postulated that Bright's disease was in fact due to a primary generalized deposition of "hyaline fibrinoid" in arterioles and capillaries. This arteriolar change, in turn, resulted in both hypertrophy of the left ventricle and contracted kidneys. In 1874, Mahomed (11) was the first to state that hypertension could occur without primary renal disease, that arteriocapillary fibrosis began as generalized hypertensive (not nephrogenic) lesions. Although the ophthalmoscope was developed by Helmholtz in 1851, a clear description of the constricted retinal vessels as related to hypertension was not described until 1876, by Gowers (12).

The physician principally responsible for popularizing the concept of hypertensive disease was Sir Clifford Allbutt. In 1895 he presented his views on "senile plethora" and "hyperpiesia" as a generalized primary vascular disease separate from glomerulonephritis (13). This was not original, since he was using the concepts previously developed by Mahomed. Although he had little new to contribute, he wrote well and spoke well, which won him fame and a knighthood. Allbutt also separated hyperten-

sive vascular disease from arteriosclerosis, stating that hypertension could occur without arteriosclerosis and vice versa.

In Germany, Frank (14) used the terms *white* and *red hypertension* to distinguish the two forms of primary renal as compared to primary generalized arteriosclerotic disease. Also in Germany the latter was named *hypertonie essential*, which might be freely translated as "primary hypertension." Unfortunately, many physicians interpreted the term to mean that hypertension was an essential adaptive reaction, a concept that discouraged any attempt to lower the blood pressure. This led to the confusing term *essential hypertension.* A more accurate term was given by Janeway (15), who, in 1913, described the varied course of hypertension and called the disorder "hypertensive cardiovascular disease."

THE MEASUREMENT OF BLOOD PRESSURE

Real progress in understanding hypertension and its treatment came with the measurement of BP quantitatively, beginning with the studies of a small-town parson in eighteenth-century England. Stephen Hales performed his now-famous BP experiments in his backyard using horses. The animals were tied down to a wooden gate without anesthesia (16). A brass pipe was inserted into the carotid artery connected to a vertical glass tube by a flexible connection made from the windpipe of a goose. While a servant stood on a chair to hold up the tube, the blood rose 9 feet 6 inches in height initially and then gradually fell. The animals died when the blood in the tube fell to approximately 2 feet.

Fifty years after Hales measured BP directly, Poiseuille (17) introduced the mercury hydrodynometer, thereby greatly reducing the height of the column needed for measuring the blood pressure. In 1864, Carl Ludwig (18), the great German physiologist from Leipsig, added a float to Poiseuille's mercury manometer with a connecting arm, which inscribed the arterial pulse wave on a moving smoked drum, thereby making a permanent record.

Essential hypertension as a clinical entity was clearly defined, however, only after the development of noninvasive methods for measuring BP in humans, which occurred at the beginning of this century. Since hypertension is an asymptomatic disorder, its recognition in humans depended upon the development of a simple noninvasive instrument for recording the level of blood pressure in the doctor's office. The early indirect attempts proved to be impractical. They were mostly aimed at measuring the systolic BP only, by determining the force required to obliterate the pulse. For example, von Basch (19), in 1880, employed a mercury-filled manometer with a rubber bulb resting on the radial artery.

He recorded the systolic blood pressure as the force required to obliterate the pulse. In 1889, von Helmholtz made important improvements in the von Basch instrument; this led him to find, for the first time, hypertension in the radial and temporal arteries but not in the dorsalis pedis artery in coarctation of the aorta, which he also correctly surmised caused the left ventricular hypertrophy found in this disorder.

The next important step was made by Riva-Rocci (20). In 1896, he developed a wraparound inflatable rubber cuff to occlude the artery in the upper arm. Subsequently, von Recklinghausen (21) increased the width of the cuff from 5 to 14 cm to obtain better accuracy on the adult arm. Riva-Rocci recorded only the systolic blood pressure, which he determined by using the first pulse that he could palpate as the cuff was slowly deflated.

The landmark breakthrough, which made blood pressure measurement a routine office procedure, came from Nikolai Sergeyevich Korotkoff (22). In 1905, he described the sounds that he heard with a stethoscope placed over the brachial artery below the Riva-Rocci-von Recklinghausen inflatable cuff during its slow deflation. Korotkoff was a privatdocent at the Imperial Military Medical Academy of St. Petersburg when Pavlov was a professor of physiology. Unlike the lengthy reporting style of his time, Korotkoff's communication was very succinct, covering less than two pages. In it he described the phases of the sounds and their probable origins based on his animal experiments. He also clearly defined the sounds that indicated systolic and diastolic blood pressure. Clinical recording of blood pressure then spread rapidly throughout the world.

FORERUNNERS OF MODERN TREATMENT

Another highly important development at that time was the discovery of renin by Tigerstedt and Bergman (23), the Scandinavian researchers who, in 1897, demonstrated a pressor principle in kidney extracts. Their pioneering effort led to the later discoveries by Goldblatt et al. (24), Page et al. (25), and Braun-Menendez et al. (26). These fundamental advances led to the surgical correction of renovascular hypertension. In addition, the discovery of the renin-angiotensin system led to the recent development of a series of important antihypertensive drugs, the converting-enzyme inhibitors.

Low-Salt Diets

The importance of salt in the diet was discovered in 1904 by Ambard and Beaujard (27), who were then medical students in Paris. Their emphasis was on chloride. However, in reducing dietary chloride they were also restricting sodium, which is probably more important in

hypertension control. Their observations preceded the use of diets extremely low in salt, which became popular in the 1940s. The success of these diets stimulated the development of the thiazide diuretics.

Several investigators, such as Watkin et al. (28) and Murphy (29), found that the rice diet of Kempner (30) depended on severe sodium restriction to levels as low as 20 to 30 mEq/day. Moderate salt restriction (as is often prescribed today) was ineffective in these patients, possibly because they all had severe hypertension. Whether moderate restriction (approximately 80 mEq/day) is effective in milder forms of hypertension remains a controversial question: some investigators claim that it is (31–33), whereas others claim that it is not (34–36).

Several investigators of the rice and fruit diet found that the marked sodium restriction leads to a reduction in plasma and extracellular fluid volume, which, in turn, is associated with the fall of BP (28,29). Extracellular fluid volume was reduced about 1 to 2 L, and plasma volume was reduced by approximately 500 ml. Dustan et al. (37) and ourselves (38) independently found a similar reduction of plasma and extracellular fluid volumes during treatment with thiazide diuretics. This suggests that the antihypertensive mechanism in both of these interventions is probably volume-dependent. It also suggests that sodium deprivation will probably not be very effective unless it is restrictive enough to cause some volume depletion (28,29,38,39).

Surgical Sympathectomy

The vasoconstrictor and cardioaccelerator properties of the sympathetic nervous system had long been known, but it was Kraus who urged the surgeon Fritz Bruening (40) to perform the first sympathectomy operation for hypertension in 1923. More extensive operations were developed by American surgeons in subsequent years, including Peet (41), Smithwick (42), and others. The experience with surgical sympathectomy led to the development of drugs producing chemical sympathectomy. These ganglion-blocking agents included tetraethylammonium chloride (43), hexamethonium (44), pentaquine (45), bretylium (46), and others.

THE BEGINNINGS OF DRUG TREATMENT

Prior to World War II there were no effective antihypertensive drugs. Sodium thiocyanate was first used by Treupel and Edinger (47) in 1900 and sporadically thereafter, including Hines (48) at the Mayo Clinic. Its effectiveness was not demonstrated by controlled trials, and it was potentially toxic. Blood level measurements were required in order to keep the dosage within a safe range; even then, side effects were not infrequent. For these reasons the drug never became popular.

Drug treatment, however, was held back primarily by the prevailing attitude of therapeutic nihilism, popularized and given respectability by most leading medical authorities. Well into the 1960s, some experts in the field believed that the arterial disease was the cause of the hypertension, rather than the result (49). The prevailing opinion scoffed at the use of drugs as "treatment of the manometer rather than of the patient." The frequent toxicity associated with the early drug treatment of hypertension only reinforced this opinion.

To my knowledge, the first effective drug treatment of malignant hypertension was in 1947 with the use of the World War II antimalarial agent, pentaquine. At that time, the head of the Squibb Institute for Medical Research, which developed pentaquine, was James Shannon, who later became the first director of the National Institutes of Health. During the preclinical testing phase, it had been found that large oral doses of pentaquine led to a reduction of BP with severe orthostatic hypotension. Shannon proposed that Squibb should initiate a program to develop drugs that would lower BP, of which pentaquine would be the first example. To carry out the clinical portion of the program he turned to Chester Keefer, chairman of the Department of Medicine at Boston University, where I was a medical resident. Keefer asked me to test pentaquine and subsequent drugs, if any, in hypertensive patients.

In 1946, I gave pentaquine to 17 patients with moderately severe to severe hypertension, including three with malignant hypertension (45). All patients were hospitalized for the therapeutic trial. After several days of treatment, supine blood pressure fell 10% to 40% below the baseline level (Fig. 1). Orthostatic hypotension was often severe at first but was usually moderate with continued administration of the drug. Side effects, however, were especially troublesome, consisting of abdominal pain and tenderness, back and chest pains, facial pallor, anorexia, nausea and vomiting, and constipation or diarrhea.

The three patients with malignant-phase hypertension showed reversal of their neuroretinitis, relief of headache, and clearing of congestive heart failure; however, there was no improvement in renal failure, which was already far advanced. Hemodynamic studies disclosed a reduction of sympathetic vasopressor reflexes such as orthostatic hypotension, inhibition of the Valsalva overshoot following a forced expiration, and abolition of skin temperature gradients from foot to abdomen. Two years later, Page and Taylor (50) reported on reversal of malignant hypertension using pyrogen therapy. However, side effects also limited its use.

Pentaquine represented an important step toward effective treatment, because it demonstrated for the first time that some of the pathological manifestations of malignant hypertension were reversed by reducing BP with drug treatment and that amelioration of less severe forms
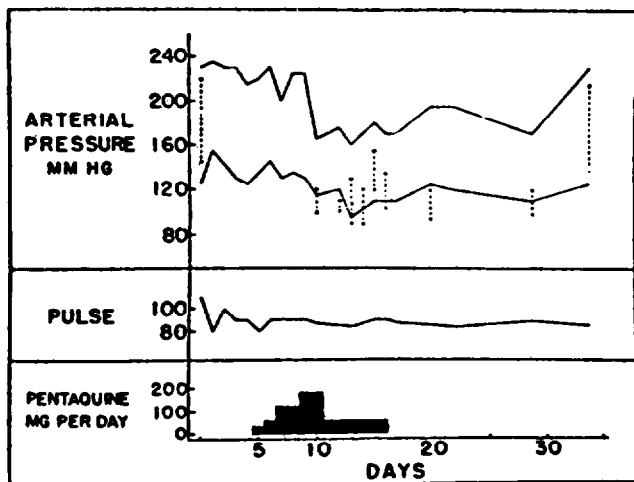
FIG. 1. Response to pentaquine in a patient with severe hypertension. The drug was increased, by daily increments, to a dose of 200 mg/day, at which point supine BP fell from approximately 230/130 to 170/105 mm Hg. The *dotted vertical lines* represent BP in the orthostatic position. Following discontinuation of pentaquine the BP gradually rose over a period of 2 weeks, to pretreatment levels. (From ref. 45, with permission.)

of hypertension might occur with the same approach. Our results with pentaquine, therefore, were contrary to the prevailing opinion that reduction of BP, per se, was not beneficial and they also encouraged the development of new drugs with fewer side effects for the treatment of hypertension.

Ganglion-Blocking Drugs

Interest in the ganglion-blocking drugs began with the observations of Acheson and Moe (51), who demonstrated in animals that tetraethylammonium blocks transmission of autonomic nerve impulses. In 1947, Lyons et al. (43) reported on studies in patients. Because of the need for parenteral administration and especially because of its brief duration of action, it was not a practical drug for treating hypertension; Lyons et al. recommended the drug primarily for evaluation of sympathetic activity in selecting patients for surgical sympathectomy and for the treatment of causalgic states.

Hoobler et al. (52) described the hemodynamic effects of tetraethylammonium. Following intravenous administration of the drug, they found a marked increase in blood flow to the extremities, particularly to the foot. Digital skin temperature rose to equal that of the thigh. Vasodilatation was not found in the sympathectomized extremity, proving that the effect of the drug on limb blood flow was due to sympathetic blockade.

More potent and longer-acting ganglion-blocking agents such as hexamethonium soon were developed that completely blocked the sympathetic nerves as

judged by increases in foot blood flow (53). Hexamethonium was introduced by Paton and Zaimis (54), who described its pharmacological properties in 1948. Arnold and Rosenheim (55) used the drug in hypertensive patients only for brief periods of time and for studies on the peripheral circulation, not as a therapeutic agent in hypertension. Finnerty and Freis (56) also used the drug in patients with peripheral vascular disease. Our main objections to hexamethonium for long-term use in treating hypertension were the need for parenteral injections at least twice per day and the many side effects of both sympathetic and parasympathetic blockade.

The first published report on the short-term effects of hexamethonium in hypertension was by Burt and Graham (57) in 1950. Horace Smirk first saw the possibilities of prolonged treatment of hypertension with hexamethonium despite its side effects. In 1950, Restall and Smirk (58) described the treatment of 15 patients with severe hypertension. BP was controlled by subcutaneous injections two to three times per day. Effective dosage varied widely, from 5 to 500 mg per dose. Despite orthostatic hypotension and many other side effects that result from both sympathetic and parasympathetic blockade, Restall and Smirk reported regression of the funduscopic signs of malignant hypertension, reduction in heart size, and dramatic clearing of the signs and symptoms of heart failure. This is the response we had seen previously with pentaquine-induced reduction of BP.

Our group found that in hypertensive patients without heart disease hexamethonium reduced BP primarily by a fall in cardiac output (59). Pressures fell not only on the arterial side but also on the venous side of the circulation; that is, there was venodilatation as well as arteriolar dilatation. By contrast, in patients with congestive heart failure the cardiac output increased (59). The marked improvement in cardiac failure was not limited to hypertensive patients but also included those with other forms of heart disease (60).

We interpreted our results (60) as follows:

Hexamethonium may interrupt the congestive failure cycle at two points: (1) By decreasing the total peripheral resistance the work demand on the left ventricle is lessened [previously the entire emphasis was on reducing the overloaded right side of the heart with phlebotomy, venous tourniquets, and the like]. (2) Also, by reducing the filling pressure of the right heart the overloaded right ventricle is able to contract more effectively. These data supply evidence that the degree of constriction of the peripheral vessels both arterioles and veins may have an important influence on the function of the failing heart. [Fig. 2]

Our data suggested that decreased BP and afterload were important in treating heart failure. This concept passed unnoticed by the medical community until 20 years later, when it was rediscovered by Cohn (61) and others (62)—although similar findings and conclusions had

DIMINISHED CARDIAC OUTPUT

CARDIAC WORK INCREASED DEMAND

OVERLOADING

INCREASED PERIPHERAL RESISTANCE

BLOOD VOLUME SHIFT TO LARGE VEINS

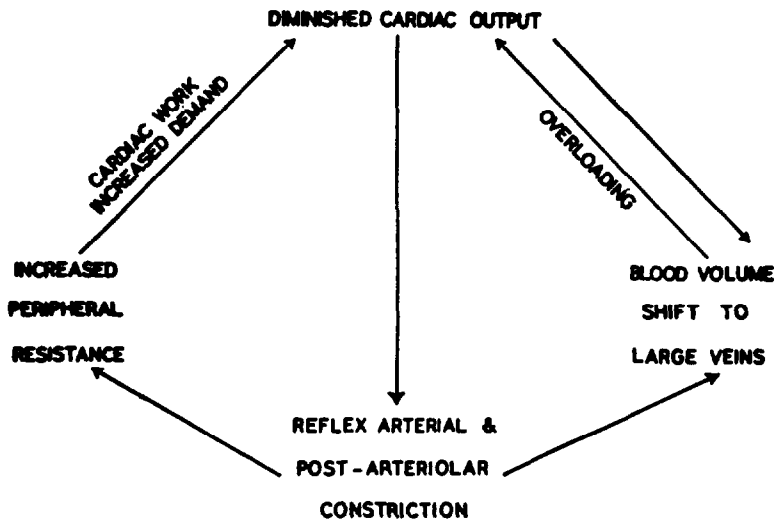REFLEX ARTERIAL & POST-ARTERIOLAR CONSTRICTION

FIG. 2. Chart illustrating concept of combined effects of arteriolar resistance (increased afterload) and postarteriolar constriction (increased preload) in establishing a "vicious cycle" in the failing heart, which was reversed by blocking the alpha-sympathetic system to both arterioles and veins with hexamethonium. (From ref. 60, with permission.)

also been made simultaneously with our report by Brod and Fejfar (63).

Hexamethonium also provided us with a vivid picture of the critical importance of the sympathetic nervous system in stabilizing the BP in the face of minor degrees of blood loss. In supine subjects following hexamethonium blockade, we removed blood by venesection into a blood transfusion bottle. With each 50 ml of blood taken from the patient there was a definite fall in BP, and when only approximately 350 ml was removed the BP had fallen to collapse levels (Fig. 3). We then rapidly reinfused the blood, and with each increment returned there was a corresponding rise of BP. When all the blood had been returned the BP was restored to the baseline level (64). Therefore, in the presence of sympathetic blockade,

blood pressure rises or falls in direct proportion to even minor degrees of blood loss that would have no effect when the sympathetic nervous system is able to respond.

Veratrum Viride, Hydralazine, and Reserpine

Veratrum viride is a shrub found in the foothills of the Allegheny mountains and elsewhere. In the nineteenth century, tincture of Veratrum viride was used by some American physicians to soften and slow the pulse (the former being due to a large fall in BP) in patients with febrile illnesses (65).

Veratrum produced an initial decrease in BP, heart rate, and regional blood flow followed within a few min-

ARTERIAL PRESSURE-MM HG

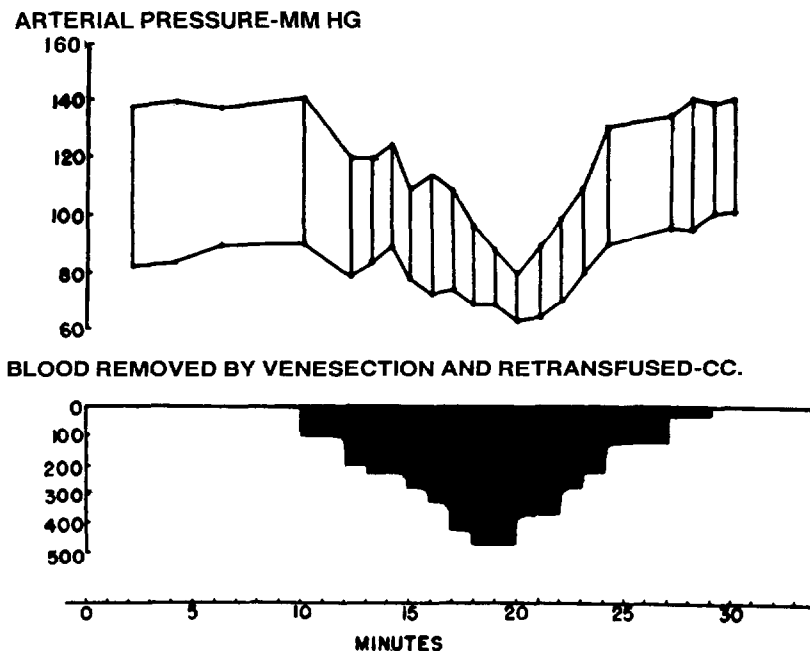**BLOOD REMOVED BY VENESECTION AND RETRANSFUSED-CC.**

MINUTES

FIG. 3. Chart of arterial pressure and of the amount of blood removed by venesection and retransfused following administration of hexamethonium (50 mg, IV). With the sympathetic nervous system blocked, there was a stepwise decrease of BP, beginning with the first 50 ml removed. With reinfusion of blood, BP paralleled the volume of blood reinfused. There was no evidence of "compensation" as occurs with an unblocked sympathetic nervous system. (From ref. 64, with permission.)

utes by a further decrease in arterial pressure and heart rate and a return of hepatic, renal, and muscle blood flows to essentially normal values. Unlike hexamethonium, cardiac output remained unchanged after *Veratrum* while total peripheral resistance fell (67). Side effects limited its clinical use.

Hydralazine was developed soon after the introduction of the ganglion-blocking agents. It was first studied by Reubi (68), who found that it was a vasodilator that increased renal blood flow. Hemodynamic studies indicated that as blood pressure fell, cardiac output increased while central venous and right heart pressure rose (69). These findings suggested that hydralazine dilates only the arterial side of the circulation and not the veins. In fact, the latter probably constrict through activation of the sympathetic nerves via the baroreceptors. This results in the unusual combination of (a) arteriolar dilatation due to direct drug action and (b) venoconstriction due to reflex action—resulting in a rise of venous pressure and, therefore, an increase in the preload of the heart.

Whereas some physicians abandoned hydralazine because of the toxicity observed with high doses, we and others found that severe toxicity need not occur if doses are restricted to less than 200 mg/day. Hydralazine is only occasionally used today, usually for specific conditions such as toxemia of pregnancy.

Reserpine appears to be a much underrated drug. Although it can produce side effects such as stuffy nose, depression, and impotence, these appear to be uncommon with low doses (70). In combination with a diuretic, it is one of our most effective antihypertensive regimens. The effectiveness of this combination has been demonstrated in several Veterans Administration cooperative studies (70,71). Furthermore, its effectiveness remains unchanged if the dose is reduced from the usual 0.25 mg/day to a dose of 0.1 mg/day (70), thereby further minimizing side effects. One thiazide-reserpine combination tablet daily containing 0.1 mg reserpine and 25 or 50 mg hydrochlorothiazide should be an ideal treatment in Third-World countries because it is not only effective in a high percentage of patients, it is simply administered, being given in a fixed dose once daily, and it is also by far the least expensive of all effective antihypertensive regimens.

THE MODERN ERA OF ANTIHYPERTENSIVE DRUGS

Thiazide Diuretics

The most important breakthrough in the history of the drug treatment of hypertension came with the discovery of the orally effective diuretic, chlorothiazide. The thia-

zide diuretics were discovered by Beyer and Sprague (72). In hypertensive patients chlorothiazide was effective in reducing BP and produced the same volume changes (37,38) as the strict low-salt diet (28,29). Furthermore, the drug was much more acceptable to the patients than a strict diet (73).

Chlorothiazide was not only effective when used alone but it also enhanced the antihypertensive activity of other drugs. This permitted smaller and less toxic doses of the latter drugs, thereby allowing effective BP control in most patients with greatly reduced side effects. Because of these properties, the drug treatment of hypertension came of age. Despite a number of excellent drugs, that have been developed in subsequent years, the thiazides remain among the most effective. The current fear of hypokalemic effects of thiazides on the heart or of long-term elevation of cholesterol appears to be unfounded (74). The diuretics are the only drugs that reduce extracellular volume. This appears to be a most important mechanism for controlling BP over the long term.

An interesting feature of the hemodynamic effects of thiazide diuretics is that although the early reduction of BP is associated with a fall in cardiac output, this becomes converted after approximately 1 month to a fall in total peripheral resistance and a rise in cardiac output, back to pretreatment levels (75).

Ledingham and Cohen (76), Borst and Borst (77), and Guyton et al. (78) demonstrated the opposite effect during the development of salt-loading hypertension; cardiac output rose resulting in a high-output, normal resistance type of hypertension. After 1 to 2 months, however, total peripheral vascular resistance increased and cardiac output fell, returning to normal, resulting in the high resistance type of chronic hypertension seen clinically. The mechanism of these late changes is unknown. It has been called "delayed autoregulation" in the case of salt-loading hypertension (78) and "reverse autoregulation" (83) in the response to diuretics.

Guanethidine and Alpha-Methyldopa

Guanethidine is a selective blocker of the peripheral sympathetic nervous system (80). This drug was never well accepted because of difficulty in adjusting dosage to avoid orthostatic hypotension. Guanethidine also had some unusual side effects, including (a) retrograde ejaculation into the urinary bladder and (b) urgency of defecation due apparently to unopposed parasympathetic activity.

Alpha-methyldopa represented the first centrally acting sympathetic inhibiting drug (81). It is less frequently prescribed today because of the development of more effective drugs.

Beta-Adrenergic Blocking Drugs

Prichard and Gillam (82) were the first to demonstrate the effectiveness of the beta-blocking drugs in hypertension. Some physicians preferred them to diuretics as primary therapy. Some beta blockers are more cardio-selective than others, some have sympathomimetic effects, and others (such as labetolol) have additional α-adrenergic blocking effects.

Converting-Enzyme Inhibitors

The development of the converting-enzyme inhibitor captopril represents a major advance in antihypertensive drug treatment. Ondetti and his colleagues (84) in 1977 reported the synthesis of an inhibitor that blocks the enzyme that converts inactive angiotension I to active angiotension II. This class of compounds has since gained wide application in controlling hypotension and in treating congestive heart failure.

A Veterans Administration study demonstrated that captopril was as effective in small doses as in large doses (85). The study also demonstrated that when hydrochlorothiazide was added to captopril the fall in BP was significantly greater than with captopril alone and was without side effects of faintness, weakness, or impotence.

Calcium Channel Blockers

Calcium ions play an important role in many biological processes, including vascular smooth muscle contraction. A number of calcium channel blockers are effective vasodilator antihypertensive agents such as nifedipine, verapamil, and diltiazem. They are also effective in treating angina pectoris, and verapamil, in particular, slows atrioventricular conduction. Other favorable features in the hypertensive heart include coronary vasodilatation, accelerated ventricular relaxation, and improvement in subendocardial perfusion.

PROVING THE EFFICACY OF ANTIHYPERTENSIVE DRUG TREATMENT

The effectiveness of antihypertensive drug treatment in preventing cardiovascular complications is based on the theory that the elevated blood pressure, per se, produces reactive hyperplastic and hyaline fibrotic changes in the arteries and arterioles as well hypertrophy of the left ventricle. During the predrug era it was believed that the vascular structural alterations were the initial change causing increased peripheral resistance, which in turn produced hypertension. The general acceptance of this concept of a secondary role for the hypertension became the basis for denying the value of reducing the blood pressure.

Others believed that hypertension began as a functional, not structural constriction of the arterioles. The structural changes followed later as a reaction to the increased blood pressure. By lowering BP the vascular disease could be arrested or, perhaps, reversed.

Although drugs for lowering blood pressure were available in the 1950s and 1960s it had not been determined whether they could reduce morbidity and mortality in hypertensive patients (86). Except for the malignant phase of hypertension most physicians were reluctant to treat patients with less severe degrees of the disorder. This opinion was reversed, however, by the results of the Veterans Administration (VA) Cooperative Study reported in 1967 (87) and 1970 (88). This controlled trial established beyond any reasonable doubt that the complications of moderate to severe essential hypertension were preventable by lowering the blood pressure with antihypertensive drugs. The VA studies were widely publicized by the National High Blood Pressure Education Program, an agency established by the then Secretary of Health, Education, and Welfare, Elliot Richardson.

The Veterans Administration trial demonstrated that in patients with initial diastolic BP between 90 and 114 mm Hg the risk of developing a major cardiovascular complication over a 5-year period was significantly reduced with treatment as compared with placebo (Fig. 4). However, the results were favorable but not significant in the subgroup patients with mild hypertension between 90 and 104 mm Hg diastolic. Results in the mild group were indecisive probably because of the fewer complications occurring in mild hypertension, which required a larger sample size than was available in the VA trial. This opened the way for larger trials focusing on mild hypertension.

The Australian trial (89) found that treatment was significantly effective in preventing stroke and was marginally effective in reducing coronary heart disease (CHD) at all levels of entry diastolic BP from 95 to 109 mm Hg. The less well-controlled Hypertension Detection and Follow-up Program (HDFP) reported that treatment was effective in reducing cardiovascular mortality including CHD at diastolic BP levels of 90 to 104 mm Hg (90). The largest study, the well-controlled Medical Research Council (MRC) trial (91), concluded that although treatment of patients with entry diastolic BP of 90 to 109 mm Hg was effective, the benefit was small in mild hypertension. There was a significant reduction in stroke in the treated group but not in CHD. Considering these and other trials it seems probable that treatment is effective in mild diastolic hypertension.

More recent trials have demonstrated equally if not more effective reduction of complications in elderly patients with hypertension. The MRC trial in over 4,000 patients ages 65 to 74 years showed significant reduction in both strokes and CHD in patients receiving thiazide
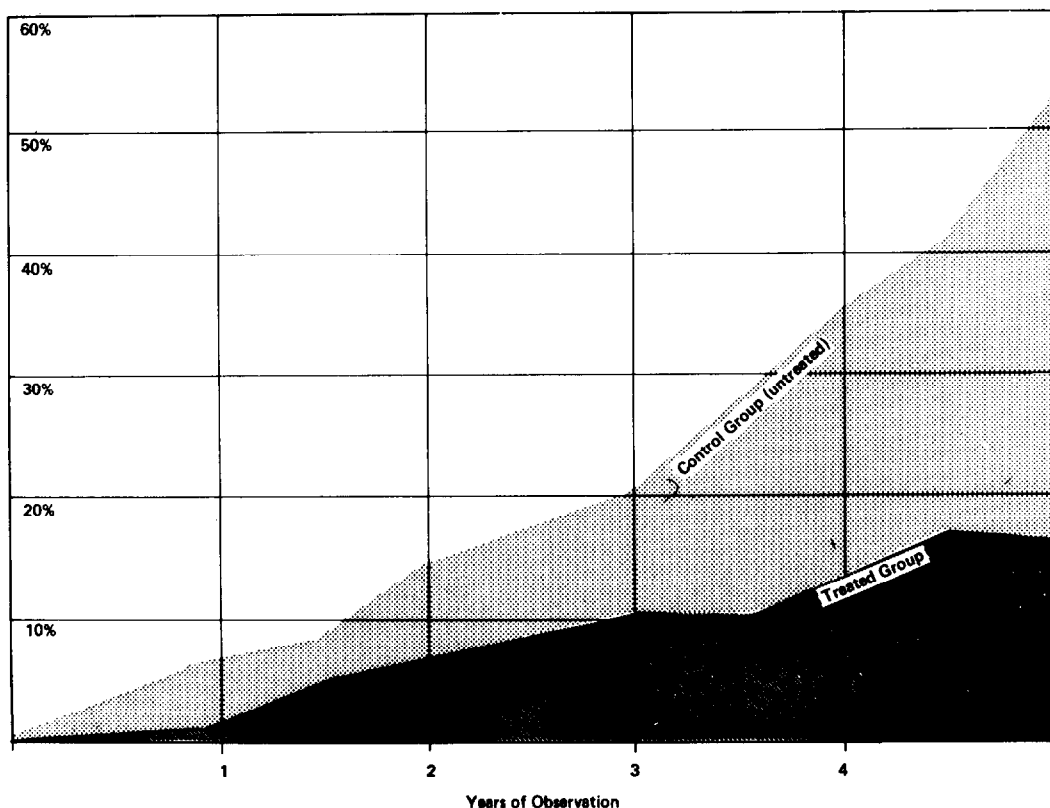
FIG. 4. Estimated cumulative incidence of major cardiovascular morbidity over a 5-year period as calculated by the life-table method. There is an increasing difference in morbidity-mortality over 5 years (55% versus 18%) between the control and treated groups, representing a 67% effectiveness of treatment (37/55). (From ref. 87, with permission.)

plus amiloride but not in those treated with the beta blocker atenolol (92). In the STOP (Swedish trial in old patients)-Hypertension trial in the elderly the reduction in complications with treatment was seen at all age groups including those 80 to 84 years old (93). The SHEP (systolic hypertension in the elderly program) trial investigated the effectiveness of treatment in elderly patients with isolated systolic hypertension (94). Stroke was reduced by 30 events per 1,000 patients. Thus, drug treatment has been shown to be effective in aged as well as younger patients. Furthermore, the treatments were well tolerated despite the patients' age.

It is important to point out an additional benefit of treatment. Prior to the development of effective antihypertensive therapy many patients, especially the young and middle-aged, developed rapid progression of their hypertension. This often culminated in malignant hypertension or some other severe complication such as renal failure, congestive heart failure, or aortic dissection. Death usually occurred within a matter of months after the diastolic BP reached 140 mm Hg or more. Such patients were formerly often seen on the hospital wards but are rarely encountered today. The effectiveness of preventing this problem has not been studied in the various clinical trials because untreated control patients exhibit-

ing progressive elevations of BP have been promptly removed from the trial and treated openly with antihypertensive drugs, thus preventing further progression of the hypertension to severe levels. This successful prevention of progression to severe hypertension is one of the most important benefits of antihypertensive treatment.

The various control trials have demonstrated that antihypertensive drug treatment is effective in reducing the cardiovascular complications of hypertension. This demonstration provides strong evidence that morbidity and mortality are the result of the elevated BP per se, and not to primary cardiovascular changes independent of the BP. Although the fundamental pathogenetic factor or factors that initiate hypertension are still unknown the cause of the complications has been clarified. It is the hypertension itself.

SUMMARY AND CONCLUSIONS

A method for measuring BP clinically was discovered less than 100 years ago. Prior to this, the disorder that we now call hypertension could be suspected only by the quality of the pulse. In ancient times a hard pulse—that is, one that was difficult to compress—was often treated with bleeding and leeches, which resulted in at least a

temporary reduction of BP. In 1827, Bright (9) recognized an inflammatory disorder of the kidney that caused a generalized cardiovascular disease leading to dropsy, apoplexy, and uremia. Later, Mahomed (11) and Allbutt (13) described a primary, generalized, fibrosis of the arterioles that did not originate in the kidney—a condition that we now recognize as essential hypertension.

In 1905, Korotkoff (22) developed a clinically applicable method for measuring BP. This landmark discovery permitted epidemiological studies of BP in relation to cardiovascular mortality. It was primarily the Society of Actuaries (95) who, in the 1920s, recognized the great prevalence and high risk of the disorder. Although it was clear to the insurance companies that a diastolic BP of 95 mm Hg or higher shortened life because of cardiovascular complications, their data relative to mild and moderate hypertension were dismissed by most physicians of the time. However, definitive proof was eventually provided by Kannel and coworkers (96) in the classic Framingham Study, which demonstrated beyond any doubt the importance of hypertension as a cardiovascular risk factor.

Except for rest and sedatives (which had no real antihypertensive effect), hypertension remained an untreated disease until the 1940s, when sympathectomy and the rice diet were advised for patients with severe hypertension. The first successful use of antihypertensive drugs in causing remission of malignant hypertension occurred in the late 1940s—initially with pentaquine and a few years later with hexamethonium.

The early drugs had many side effects and it was not until the 1950s that the first breakthrough occurred with the development of chlorothiazide. This drug was highly effective orally, it was well tolerated, and it enhanced the antihypertensive effectiveness of other drugs when given in combination with them. The beta blockers represented the leading advance of the 1960s, followed in recent years by the converting-enzyme blockers and the calcium-channel blockers as major therapeutic agents.

As recently as 25 years ago the effectiveness of antihypertensive drug treatment of moderate essential hypertension was still disputed. The issue was finally settled by a controlled clinical trial, the Veterans Administration Cooperative Study, which demonstrated beyond any reasonable doubt that drug treatment was effective in preventing the complications of moderate hypertension (diastolic BP of 105 mm Hg and above). Large-scale trials followed, which determined that treatment was also effective in mild asymptomatic hypertension (diastolic BP of 90–104 mm Hg). Other trials demonstrated the effectiveness of treatment in elderly patients, including those with isolated systolic hypertension.

It is remarkable that it has taken less than 90 years from the time high blood pressure was first recognized clinically to the present period of effective control. Coronary heart disease is the most common cause of death in hypertensive patients. Reduction of BP generally has been less successful in preventing myocardial infarction than in preventing stroke. It seems probable that with simultaneous reduction of other risk factors for coronary heart disease we may look forward to greater effectiveness in treating this most important cause of death in hypertension.

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