

## Hypertension: A controllable disease

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It is an especial pleasure for me to receive this award which honors Dr. Oscar B. Hunter whose name and reputation is so well known and well respected in my home city of Washington, D. C.

My first experience with antihypertensive drug treatment was in 1946, when as a research fellow at the Evans Memorial Hospital in Boston, I used the antimalarial drug pentaquine to treat malignant hypertension and other forms of severe hypertension. Dr. Smithwick was chief of surgery there at that time and I was referred the patients whom he rejected for his operation of lumbodorsal sympathectomy. In doses larger than those used in the treatment of malaria, pentaquine exhibits sympathetic blocking activity. Although it was fairly toxic in these doses and had a number of disagreeable side effects including methemoglobinemia, pentaquine

did reduce the blood pressure effectively in some of these patients.<sup>2</sup> It was exciting to see that along with the reduction of blood pressure there was clearing of hemorrhages, exudates, and papilledema in the optic fundi and disappearance of the manifestations of malignant hypertension except for the uremia.

At that time the accepted theory indicated that hypertension was a manifestation of a generalized disease. It was not thought that the hypertension could in itself be the cause of end-organ damage. Therefore, it was not considered rational that reduction of blood pressure would favorably affect the course of the disease. Antihypertensive therapy was scornfully referred to as treating the manometer rather than the patient. A reason for under-rating the importance of the blood pressure was the very poor understanding of the lability of blood pressure. It was assumed that the blood pressure exhibited by an anxious patient made more apprehensive by a visit to the physician was representative of the blood pressure existing at all times in that individual. Thus, there seemed to be no direct correlation

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between level of blood pressure and presence of end-organ damage. In those days I frequently heard the comment, "You know, I have a patient who is now 80 years old. She has had a blood pressure of 230/130 for the past 25 years and she is still quite well and probably a good deal happier than if she had been taking one of your drugs." It was not mentioned that during the course of a hospitalization the blood pressure of this patient fell to 130/80 shortly after admission; the latter reading probably was closer to her average blood pressure. Also physicians tended to forget the many other patients with persistently high levels of blood pressure who had developed complications and had died.

Meanwhile, I kept running across other evidence that strengthened my conviction that it was the elevation of blood pressure per se which caused target organ damage. For example, severe pulmonary hypertension such as results from a widely open ventricular septal defect was associated with sclerosis of the pulmonary arterioles. In Goldblatt's hypertension, Wilson and Pickering<sup>10</sup> and Wilson and Byrom<sup>9</sup> showed that nephrosclerosis developed in the opposite kidney exposed to the high pressure, while the kidney with the clamp on the renal artery was relatively protected from such damage. I recall being told of a patient who developed hypertensive neuroretinopathy in one eye and not in the other. Later it was found that the carotid artery was occluded on the side which remained normal. Coarctation of the aorta results in left ventricular hypertrophy and dilatation but does not cause nephrosclerosis. Thus, both the vascular and cardiac manifestations of hypertension seemed to be the direct result of an elevated blood pressure.

It was a good example of how wrong traditional medical thinking can be and still be well enough entrenched to resist obvious clinical and experimental evidence to the contrary. Medical opinion is most dangerous when it is most respectable.

The Osler tradition of therapeutic nihilism was very popular. It was respectable to diagnose. It was not respectable to treat unless one knew the cause, and medical opinion would not entertain the possibility that the cause of hypertensive complications was the hypertension itself. Oddly enough, it was considered respectable to lower the elevated blood sugar in diabetes, although the evidence now indicates that this is not useful in preventing the vascular disease associated with diabetes. It should be noted that controlled clinical trials were required to destroy both of these false conceptions, one in hypertension and the other in diabetes.

Another refutation of traditional thinking became clear to me as a greater variety of antihypertensive drugs became available for testing. Since hypertension is characterized by an increased peripheral resistance, I thought it was important to find drugs which lowered blood pressure by dilating the peripheral arterioles. However, as we studied the hemodynamic and clinical effects of various antihypertensive agents we found that it did not appear to make much difference therapeutically how the blood pressure was reduced. For example, we found that ganglion blocking drugs reduced cardiac output but not total peripheral resistance.<sup>3</sup> Yet, ganglion blocking drugs were as effective if not more effective in reversing the manifestations of malignant hypertension than hydralazine which was a classical example of a peripheral vasodilator.<sup>5</sup> It became increasingly clear that the key element therapeutically was to bring the blood pressure down. The mechanism by which it was reduced was not all important. It was important, however, that the drug be effective in lowering blood pressure and that it be relatively free from severe side effects.

Peripheral vasodilators, in fact, had an inherent disadvantage. Since they did not affect the cardiac sympathetics, the latter were reflexly stimulated by the fall in blood pressure through the baroreceptor

mechanism. As a result, heart rate and myocardial contractility increased. This not only made patients feel uncomfortable, but also partially nullified the antihypertensive effect of the vasodilator drug.

As a result of such experiences, I became increasingly convinced that the most effective way to treat hypertension was to use combinations of drugs. Blood pressure normally is controlled by a variety of mechanisms. These mechanisms include first, the inherent or autonomous tone of the arteriolar smooth muscle; second, the integrative activity of the sympathetic nervous system acting over the entire cardiovascular system including not only the arterioles but also the heart and veins; and, third, the fluid balance of the body is important in that an excess of extracellular and plasma volume tends to raise blood pressure while dehydration tends to lower it.

The thiazide diuretics represented a most important advance in antihypertensive drug therapy because they were not only antihypertensive in themselves but by depleting extracellular volume also greatly increased the responsiveness of the patient to other antihypertensive agents, thereby permitting lower and less toxic doses of the latter drugs.<sup>4</sup> In some patients it may be necessary to affect all of these mechanisms using in combination, a diuretic, a peripheral vasodilator, and a sympathetic inhibitor. The combination of chlorothiazide, hydralazine, and reserpine is an example of this approach.

The final proof of the effectiveness of antihypertensive drug treatment in preventing end-organ damage in benign essential hypertension as well as in malignant hypertension was provided by the controlled therapeutic trial carried out by my colleagues and me in the Veterans Administration study.<sup>7, 8</sup> Very briefly, this study was a prospective, randomized, double-blind trial, comparing drug and placebo treatment in male hypertensive patients with persistent diastolic elevations between 90 and 129 mm Hg. The inci-

dence of hypertensive complications such as stroke, congestive heart failure, accelerated hypertension, progressive renal damage, and dissecting aortic aneurysm was greatly reduced in the drug-treated as compared to the placebo-treated group. Only the incidence of myocardial infarction appeared to be unaffected although even here fatalities due to coronary artery disease seemed to be less in the drug-treated group.

The VA trial was of great significance in erasing any lingering doubts concerning the therapeutic value of antihypertensive drug treatment. Also, although long-term, large-scale cooperative trials in outpatients are difficult to accomplish, the VA study demonstrated that it is possible to use this technique successfully to demonstrate the value of an effective form of treatment. To be successful, however, in my opinion rigorous selection of adherent patients is essential. Also, careful planning and persistent effort are required to assure success. Long-term cooperative trials are the most difficult but they also may be the most rewarding of all experimental procedures in medicine. They are evolving into a powerful tool for settling important therapeutic questions.

Before concluding, I would like to present some current work which is related to the general field of antihypertensive agents. However, in this instance they are used as experimental tools to explore the nature of congenitally transmitted hypertension. As you know, essential hypertension is a strongly inherited characteristic. Recently, the Japanese have developed a strain of rats in which the hypertension is congenitally transmitted.<sup>6</sup> As these rats approach adult life they begin to develop hypertension which becomes progressively more elevated with the passage of time. Blood pressures are higher in males than females and after one year of age the former begin to die off from the complications of hypertension. The Japanese have called this model of essential hypertension the spontaneous hypertensive rat (SHR).

When these animals became available in this country, I became interested in determining whether the progressive hypertension of the SHR could be modified by antihypertensive drug treatment. For some time I had been impressed by an apparent modification of the severity of hypertension following drug treatment in patients. I had the clinical impression that in some patients the hypertension became less severe after a prolonged period of effective antihypertensive treatment. The availability of the SHR seemed to present an ideal opportunity to study this aspect of hypertension under controlled conditions.

Our first experiment was with an excess of salt.<sup>1</sup> The drinking water was replaced with one per cent salt solution. Excess salt administration was begun when the rats were 3 months old and continued for a period of 5 months. Blood pressure measured in the tail by the plethysmographic method indicated a steeper rise of blood pressure in the salt-treated animals, and after 4 months several already had died of malignant hypertension.

In our next experiments we treated the SHR with antihypertensive drugs. Preliminary experiments indicated that a mixture of chlorothiazide, reserpine, and hydralazine dissolved in the drinking water was extremely effective in reducing the blood pressure and did not seem to adversely affect the well-being of the animals.

Beginning at 3 months of age, we randomly selected from the same litters a group of the SHR which were treated and another group of controls who remained untreated. At 3 months of age the systolic blood pressures of the 2 groups were similar, averaging about 130 mm. Hg in each group. Treatment with antihypertensive agents was continued for 6 months and then was abruptly discontinued. During the treatment period the blood pressure fell and at the end of the 6 months averaged 92 mm. Hg. By contrast the blood pressure of the control group rose gradually to a level of 160 mm. Hg at the end of the 6 month period.

At that time, when the rats were 9 months of age, treatment was stopped and the blood pressure of the treated animals rose abruptly but not to the level of the controls. Rather it rose to the same level as had existed when the treatment was started 6 months previously. Following this rapid elevation, the blood pressure rose gradually over the succeeding 4 months at the same rate and to the same level as the controls exhibited when they were progressing from 3 to 7 months of age. Thus, at 13 months of age (4 months after discontinuing drugs) the blood pressure of the previously treated rats was approximately 150 mm. Hg which is the same as the blood pressure of about 150 mm. Hg exhibited by the controls when they were 7 months of age.

These results could not be ascribed to poor condition of the treated animals. Both groups gained weight at the same rate throughout the experiment and the treated rats were active, alert, and in apparently excellent health throughout.

What is the significance of these experiments?

First, they indicate that the hypertension is not dependent upon any biological changes associated with aging *per se*. When the treatment was stopped the blood pressure did not rise to the level of the controls, which would have been the case if the hypertension was an age-dependent process. Rather it rose to the level that had existed prior to treatment, 6 months previously, when the rats were 3 months of age. Six months in the life of a SHR is equivalent to about 20 years in the life of man, and during this period the rats had progressed from young adulthood to middle age. This form of hypertension, therefore, appears to be a time-dependent rather than age-dependent process. Over time the blood pressure builds gradually on the previous base somewhat in the fashion that coral builds upon itself by gradual increments to form a reef.

Second, while the hypertension is genetically determined the rate of blood pressure increase is greatly influenced by en-

vironment. An excess of salt will accelerate the process dramatically. On the other hand, progression of the hypertension can be completely arrested for the duration of antihypertensive drug treatment. Therefore, the course of the disease can be influenced by modifying environmental factors. Thus, both genetic and environmental factors are important in determining the severity of this form of hypertension.

The animals were sacrificed when they were 13 months of age. At this time the average blood pressure of the control SHR had reached 185 mm. Hg. Many of these control animals exhibited end-organ damage in the heart, kidneys, and mesenteric arteries. The left ventricle was hypertrophied and showed small infarcts with areas of myocardial necrosis and fibrous tissue replacement. The kidneys showed nephrosclerotic changes, focal pyelonephritis, and in some cases fibrinoid necrosis of arteries and arterioles. The mesenteric arteries exhibited segmental areas of fibrinoid necrosis and extensive infiltration of the wall with inflammatory cells and fibroblasts. This resulted in a nodular or beaded appearance of the arteries resembling periarteritis nodosa.

In striking contrast none of these pathological changes were seen in the treated animals. At the time of sacrifice, the blood pressure of these animals averaged only 150 mm. Hg and apparently this was not high enough to result in end-organ damage. Thus, in these SHR, as well as in experimentally induced hypertension,<sup>9, 10</sup> it is apparent that the pathological changes are the result of the hypertension and can be entirely prevented by effective antihypertensive therapy.

In the past, it has been considered essential in the understanding and treatment of any disease that we determine first the nature of the primary pathogenetic mechanisms. In infectious diseases, for example, the approach has been to identify an organism and, by Koch's postulates, prove that it is the cause of the disease. Once the organism has been isolated, biochemical agents can be found which will

kill or arrest the multiplication of the causative microorganisms. Such a classical approach has been applied unsuccessfully to hypertension and to other disorders for many years. In hypertension the primary pathogenetic mechanism has been sought in the kidney, in the adrenals, and in the autonomic nervous system. While these extensive efforts on the part of many individuals have given us a better understanding of the physiological control of blood pressure and have been helpful in understanding some unusual forms of hypertension, they have not revealed the cause of essential hypertension nor have they been particularly helpful in the treatment of the majority of patients.

The results I have summarized today indicate that considerable progress also can be made if we set for ourselves a somewhat less ambitious goal. When the ultimate cause of a disease is obscure and there are no immediate prospects of discovering such a cause, we still can profit by devoting considerable effort to investigating, understanding, and controlling the consequences of the disease. In essential hypertension, the ultimate cause or causes remain unknown but the pathological consequences are the result of the elevation of blood pressure. Efforts at controlling the latter have paid off dramatically while basic research into ultimate cause is still largely frustrated.

A similar approach can be used in other important diseases, such as atherosclerosis. The cause of the basic lesion in atherosclerosis is poorly understood. Probably there is a basic injury to the vascular wall that we do not understand and cannot control. Yet, there also is considerable evidence that the severity and rate of development of atherosclerosis is related to the serum cholesterol concentration and to the level of blood pressure. Much more can be done to clarify the effects of these adverse influences and to test the effectiveness of modifying them in arresting the development of atherosclerosis. I have little patience with the purists who seek vainly for the needle in the hay stack looking exclu-

sively for ultimate causes. This is scientific snobbery. The primary responsibilities of medicine are to cure the sick and to prevent disease. In medical research we must work with the most promising leads we have and by so doing important progress will be made. I am not against the attempt to fulfill Koch's postulates as a useful step in finding effective treatment in all diseases, but it seems foolish to rigidly and exclusively adhere to such a purist's approach when more promising avenues of therapeutic investigation which are equally valid may be lying readily at hand.

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