

Rebuttal: Appraisal of Antihypertensive Drug Therapy

By EDWARD D. FREIS, M.D.

DR. HERBERT CHASIS has long been known for his skepticism with respect to the treatment of hypertension. Indeed, it was the skepticism of Drs. Goldring, Chasis and Perera which served as an important stimulus in planning the Veterans Administration Cooperative Study.

Dr. Chasis completely rejects the concept that the cardiovascular damage seen in hypertension is the consequence of the elevated blood pressure. To him the cardiovascular pathology is independent of the blood pressure. It follows, therefore, that anti-hypertensive therapy cannot prevent further cardiovascular damage or complications. I believe this is why Dr. Chasis makes such unusual interpretations of the available data.

His main attack is on the results of the Veterans Administration Cooperative Study. Unfortunately, he begins with an error of fact. With respect to the first report of the Veterans Administration Cooperative Study Group the numbers of patients randomized were 70 in the control group, not 63 as stated by Chasis, and 73 not 68 in the treated group. Dr. Chasis notes correctly that there were 27 patients with severe complications in the control group and only 2 in the treated group. He attempts to explain this difference by the fact that the control patients may have had more severe vascular disease prior to randomization than did the treated group.

It should be noted that patients were randomly assigned double-blind to one regimen or the other. Thus, the chance that biased selection of patients could account for the observed 27 to 2 ratio of morbid events must be of the order one in a thousand or higher. To support his contention that randomization did not establish an equal distribution Dr. Chasis notes that the patients in the control group had a high incidence of vascular disease prior to entry. Thus, 5 had preceding cerebral thrombosis, 5 had diabetes mellitus and 22 had an abnormal electrocardiogram. Dr. Chasis neglects to mention, however, that in the treatment group there also was a high incidence of preceding vascular disease as follows: 6 patients with

prior cerebral thrombosis, 8 with diabetes and 24 with an abnormal electrocardiogram. These and other data listed in tables 1 and 2 of the original paper¹ indicate that the control and treatment groups were not significantly different with respect to any risk factors. This equality was achieved purely by random assignment of regimens without any artificial attempts at "matching."

These details are important because they negate Dr. Chasis' argument that the control group was much more severe than the treatment group and that it was the difference in risk rather than the effects of treatment that explained the striking difference in outcome in the two groups. Quite to the contrary it was because of the experimental design that the conclusion is inescapable that the difference in outcome between the control and treated groups was due to the effects of treatment. This study even took the dropouts into account. When it was assumed that all of the treated dropouts had developed complications as compared to none of the control dropouts the difference between the treated and the non-treated group still was significant at $P < .001$.

Dr. Chasis next calls attention to the rapidity with which the control group patients developed complications. This he notes is widely different from the prognosis of 300 hypertensive patients followed by Perera. The severity of the hypertension in Perera's series, however, is entirely different from that of the high risk patients in the Veterans Administration Study. It is simply not possible to compare widely disparate groups. One should choose a different series more closely aligned to ours in severity such as Leishman's male control group.² His observed mortality was 66% in 12 years or 5.5% per year, the majority of the patients dying before age 60. This is a higher mortality than was observed in the Veterans Administration Study where there were 4 deaths in 20 months of follow-up.

Much of the confusion arises from the fact that Dr. Chasis fails to differentiate between the prognosis in labile as compared to more stabilized forms of hypertension. It is impossible to consider the prognosis in essential hypertension in a meaningful way unless these differences are taken into account. For example, Mathisen and his associates found that the death rate per 1000 years of observation in un-

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treated men with mild to moderate essential hypertension was 20.3 for the labile group and 99.8 or 5 times higher for the group with more stabilized diastolic hypertension.³ Labile hypertension was defined as a fall in diastolic blood pressure below 95 mm Hg during bed rest and sedation. Our patients also had persistent diastolic hypertension in that the average remained above 89 mm Hg from the fourth through the sixth hospital day. High risk patients such as were present in the Veterans Administration are not uncommon although they need to be knowledgeably identified and differentiated from the labile group.

Dr. Chasis calls attention to the nature of the 27 complicating events that occurred in the control group. He notes that 12 of these 27 consisted of either elevation of blood urea nitrogen, appearance of striate hemorrhages or cotton wool exudates in the optic fundi, or elevation of diastolic blood pressure to 140 mm Hg or higher. Dr. Chasis then makes the following astonishing statement, "These end points have the inherent weakness of representing spontaneously reversible events in the course of hypertensive disease." Spontaneous reversion, however, is decidedly rare in my experience and in the experience of most other observers.⁴ For example, Pickering emphasizes that neuroretinopathy rarely clears until the blood pressure is brought down.⁴ Prior to the treatment era when a patient developed fundoscopic changes, high diastolic blood pressure and azotemia they progressed with only rare exceptions to fatal complications within a few months to a few years.

Dr. Chasis next turns to the report on the patients with initial diastolic blood pressures of 90–114 mm Hg, the so called mild and moderate hypertensives. In this instance he does not dispute the effectiveness of treatment although we had made a special point of emphasizing that our data while demonstrating the effectiveness of treatment in patients with diastolic blood pressures of 105 mm Hg and higher left unanswered the question as to the effectiveness of treatment in patients with blood pressures in the 90–104 range.

Dr. Chasis seems to be confused about the relationship of hypertension, vascular disease and morbidity. Repeatedly he stresses that the high risk patients were those with the most vascular disease and argues that it is the vascular disease and not the hypertension that is important. This concept is dangerous because it leads to the conclusion that the level of blood pressure is unimportant. Actually, the burden of evidence today from both animal experiments and clinical studies is that it is the

hypertension which produces the vascular disease.⁴ When a patient manifests vascular disease it means he has had hypertension for a long period of time or that it has been so severe as to produce an imminent threat of a complication. The Veterans Administration Study, in essence, showed that treatment reduced that threat.

Dr. Chasis rightly calls attention to the failure of the Veterans Administration Study to demonstrate a protective effect of treatment against coronary artery disease. In our reports we were careful to point out that the results demonstrated effectiveness of treatment in "hypertensive" complications but not against "atherosclerotic" complications. However, this does not prove that a protective effect might not be demonstrable if treatment were started at a younger age and at an earlier stage of the hypertension.

Dr. Chasis also is correct in pointing out that our population of patients had more vascular disease and were at higher risk than a population that would be selected from the community at large. All of our patients had sustained hypertension in that their diastolic blood pressure averaged 90 mm Hg or higher from the fourth through the sixth day of hospitalization. They also exhibited more vascular damage and were further along in their disease than the average patient. These considerations, however, do not negate the results of the study. The point is still valid that under well controlled conditions a highly significant protective effect of treatment was found in the patients with diastolic blood pressures of 105 mm Hg or above. Further studies are needed to determine whether patients with lower levels of blood pressure will be benefited by treatment.

Untreated diastolic hypertension of 105 mm Hg or above if sustained leads eventually to vascular damage. The results of the various trials that have been carried out all agree that if the blood pressure is controlled this progression of cardiovascular disease is considerably reduced or prevented. Those who overlook, misconstrue or misinterpret these data do so at their own and their patients' peril.

References

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