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The Changing Outlook in Essential Hypertension

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Since Goldblatt's classical work on renovascular hypertension there has been a concerted effort to arrive at the etiological basis of essential hypertension. The work has been successful in uncovering the causes of a few unusual or rare types of hypertensive diseases, and has led to the realization that hypertension is a manifestation or response of the body to a variety of pathogenetic factors. Yet, the cause of essential hypertension, which represents more than 90 per cent of the hypertensive population, remains obscure. Indeed, Pickering [1] was led to conclude that no specific abnormality is present. According to Pickering benign essential hypertension represents simply the right-hand side of the bell-shaped distribution curve of normal blood pressures in the general population. The distinction between normal and hypertensive is quantitative, not qualitative. According to Pickering the separation of "normal" from "abnormal," using 140/90 mm. Hg as the dividing line, is purely arbitrary. Blood pressure levels in the general population are a continuum and one could equally well take some other arbitrary value.

Pickering's concept is supported by the accumulated experience of the life insurance companies [2] who have found that life expectancy worsens with any elevation of blood pressure above the lowest normal levels. Thus a group of individuals with blood pressures of 130/80, for example, will not live as long on the average as another group exhibiting blood pressures of 110/65. These life insurance data also bring out the important point that blood pressure and mortality are *quantitatively* related, that is, that the complications of hypertension are directly related to the absolute level of the blood pressure.

In the 1930s and 1940s almost all of the emphasis in hypertension research was directed toward discovering etiological processes. The only drug seriously proposed for controlling the disease was potassium thiocyanate and this was neither very reliable nor very safe. The only accepted therapy was sympathectomy and even here it was questioned whether the results merited the risk and discomfort associated with the operation.

In the late 1940s and early 1950s, however, a concerted chemotherapeutic attack on hypertension began, first with the Veratrum alkaloids and then with the ganglion-blocking agent, hexamethonium. Using the latter drug, Restall and Smirk [3] convincingly demonstrated that it was possible to reverse many of the manifestations of malignant hypertension. Previously, I had observed reversal of the malignant phase of hypertension using the antimalarial drug, pentaquine orally,[4] and also Veratrum viride given in daily intramuscular injections. However, these agents produced almost intolerable side reactions in the doses required and therefore did not represent a practical approach to treatment.

Antedating both of these observations, Page had found that pyrogenic renal extracts were capable of reducing blood pressure and thereby reversing the malignant phase of hypertension at least in isolated instances. For a time, the daily administration of pyrogens was an acceptable if somewhat uncomfortable method for treating malignant hypertension. Even hexa-

methonium, the most acceptable and most reliable of the various treatments, became notorious for the side-effects it produced because of the variety of symptoms resulting from both sympathetic as well as parasympathetic blockade. The "hexamethonium man" was characterized as a pale, constipated individual who felt faint in the erect position, suffered from the cold, was slow to urinate, and was totally lacking in sex.

Despite these crude beginnings, the exciting fact remained that with the exception of renal failure the observable manifestations of the most severe type of hypertension were reversible, and even in the case of the former there was evidence that the rapid progress of the renal deterioration was retarded. The impetus provided by this discovery quickly led to additional therapeutic agents. Rauwolfia serpentina was introduced from India where its use had been popularized by Vakil.[5] Hydralazine followed soon thereafter,[6] and 5 years later the important thiazide diuretics were introduced.[7] Using combinations of these less-potent but better-tolerated agents there evolved a practical, tolerable, and reasonably effective therapy for controlling elevated blood pressure.

Encouraged by the success in treating malignant hypertension, investigators began to consider a broader attack on the problem. It seemed a reasonable hypothesis that all of the disabling complications of hypertension such as cardiac enlargement, cerebral hemorrhage, dissecting aneurysm of the aorta, and nephrosclerosis were the direct result of the elevated blood pressure per se and that if one could control the hypertension early these major complications might be prevented. It even seemed possible that the incidence of atherosclerotic complications which are so common in hypertension, principally myocardial infarction and cerebrovascular thrombosis, could be reduced considerably if the blood pressure were maintained at normal levels from an early stage of the disease.

There was much indirect evidence to support this hope. An inordinately frequent association between hypertension and cerebrovascular and coronary thrombosis has been repeatedly demonstrated, most recently in the Framingham study.[8] Nature has also provided several crucial experiments in man demonstrating the causal relationship between elevated blood pressure and the development of atherosclerosis. For example, the low pressure pulmonary arterial system is almost never the site of atherosclerotic lesions; yet, in the presence of longstanding and severe pulmonary hypertension, as occurs with large intraventricular septal defects, atherosclerosis is common. In coarctation of the aorta, atherosclerotic lesions are prevalent in the high pressure area above the coarctation, whereas in the low pressure area below, the aorta may be almost completely spared. Most significantly, Deming[9] showed that experimental atherosclerosis in rats was considerably worsened if the animals were made hypertensive, but that this acceleration could be prevented if they were simultaneously treated with antihypertensive agents.

Using a working hypothesis that antihypertensive therapy prevents the complications of hypertension from developing, investigators began to collect evidence that would bear on this question. Unfortunately, the early

reports left much to be desired in the way of experimental design and, therefore, were not very convincing. Most of these reports compared a presently treated series with case records from the decade of the 1940s prior to the advent of effective antihypertensive drugs. It is little wonder that the results were conflicting and often reflected the bias of the observer. Thus, Leishman [10] reported a significant reduction in mortality in the treated patients with benign essential hypertension, whereas Perera [11] found no difference in mortality in middle-aged patients with moderately severe essential hypertension. Hodge, McQueen, and Smirk [12] used as their control the patients who refused treatment. This at least placed the control group in the same era as the treated patients but introduced an unknown bias since the untreated group probably were more neglectful of their health and were in any event essentially lost so far as control of their future therapy was concerned. These authors reported a significant reduction in mortality in Keith-Wagner Groups I and II as a result of treatment.

The first controlled trial was that reported by Hamilton [13] who alternately assigned 61 patients with diastolic blood pressures of 110 mm. Hg or higher to active treatment and placebo. Of these, 30 were treated with antihypertensive agents while 31 were not. Over an 8-year period of followup, sixteen of the untreated patients had complications, primarily strokes, as compared to five of the treated group. A prospective, randomized control study was carried out by Wolff and Lindeman [14] in 87 patients. Twelve per cent defaulted. Over a 2-year period the incidence of morbid events in the treated patients was one third of that observed in the placebo group. Both of these studies were concerned with essential hypertension of more-than-average severity. Definitive evidence on the value of treatment in the "garden variety" mild case of essential hypertension still was lacking.

In 1963, a group of interested investigators in the Veterans' Administration [15] decided to initiate a carefully designed, rigorously conducted multiclinic trial on the effects of drug treatment on morbidity in both mild and moderately severe hypertension. The population selected was the group of patients with diastolic pressures from 90 to 130 mm. Hg, who had no evidence of severe hypertensive complications.

It was realized that the patient who does not take his medications regularly could seriously distort the results. Therefore, special precautions were taken to recognize and exclude such patients from the study. This was done by instituting a 2- to 4-month prerandomization trial period, during which time pill counts and urine fluorescence tests were carried out. The latter test was based on the ability of riboflavin to cause urinary fluorescence when the urine was viewed under ultraviolet light. Riboflavin was incorporated in the placebos that were administered to all patients during the trial period. Only those patients who kept their clinic appointments, returned an acceptable number of tablets, and exhibited riboflavin fluorescence in their urine were accepted in the trial.

Following the trial period the accepted patients were randomly assigned, double blind, either to active drugs or to placebos. The active drug regimen

consisted of hydrochlorothiazide, reserpine, and hydralazine. The effectiveness of this regimen in reducing blood pressure was attested to in the patients with moderate hypertension by the fact that whereas the placebo group exhibited no significant change in blood pressure the average reduction in the actively treated patients was 43/29 mm. Hg.

After the study had been in progress for approximately 2 years it became apparent that a high incidence of complications was occurring in the segment of the placebo-treated patients whose entrance diastolic blood pressures averaged 115 mm. Hg or higher.[16] Of seventy placebo-treated patients with such levels of blood pressure on entrance, twenty-seven severe complicating events developed as compared to only two in the seventy-three actively treated patients. Four deaths occurred in the placebo group and none in the active group. The deaths were unusual in that two were associated with dissecting aortic aneurysm, one with ruptured atherosclerotic aneurysm of the abdominal aorta, and only one with the more common cause of sudden death probably due to myocardial infarction. The most common nonfatal complication in the "severe" group was the development of signs of malignant hypertension, that is, further elevation of blood pressure and the appearance of hemorrhages, "cotton wool" exudates, or papilledema in the optic fundi. All of the latter responded promptly with clearing of the malignant signs when known active treatment was started. Other less frequent complications in the placebo-treated patients were congestive heart failure, increasing azotemia, cerebrovascular accidents, myocardial infarction, and severely elevated blood pressure without neuroretinopathy. The two complications occurring in the actively treated patients was one instance of cerebrovascular thrombosis and one patient who developed multiple drug toxicities, which later disappeared when his drug regimen was changed.

It is evident from the preceding study that patients with diastolic pressures averaging 115 mm. Hg or higher during repeated office visits represent an especially high-risk group who tend to develop complications more specifically related to hypertension than to atherosclerosis. The evidence that treatment was effective in this group in preventing complications was overwhelming. Even if one accounts for the 7 per cent dropouts, and assumes that all of those who dropped out on active drugs developed a morbid event whereas none of the placebo-treated dropouts did, the evidence favoring treatment would still be significant with a probability of less than 1 in 1,000 that the difference could have occurred by chance.

In the "milder" group of hypertensive patients with entrance diastolic blood pressures averaging less than 115 mm. Hg, no highly significant difference has yet developed between the treated and placebo groups over an average followup period of approximately 3 years. Further, the types of complications developing in this milder group differ from those in the more severe group in that they are predominantly atherosclerotic with sudden death and myocardial infarction being especially prominent. Because atherosclerotic complications predominate in these milder cases one would

expect that if a significant effect of treatment will appear it will take a considerable period of time to become evident.

It has also been observed that the pattern of fatal complications has been changing in the last 15 years and that the difference is most likely due to antihypertensive treatment. Whereas, in the 1940s and previously the most common causes of death in hypertension were congestive heart failure, uremia, and cerebral hemorrhage, today the most frequent cause is coronary artery disease including sudden death which in most instances is due to ventricular fibrillation secondary to coronary artery disease. Hodge and Smirk [17] reported recently that during the years 1959 to 1964 coronary artery disease accounted for approximately half of all deaths related to hypertension. Stroke was the second most common cause of death, accounting for about one fourth of the deaths related to hypertension. Deaths due to unrelated causes, such as cancer, accounted for 18 per cent of all deaths, a considerable rise over prior decades. Deaths from uremia occurred in only 10 per cent of the total while congestive heart failure accounted for only 6 per cent of the total deaths. Now that acceleration of hypertension is prevented by antihypertensive therapy it appears that the atherosclerotic complications have emerged as the most important remaining problem in the treatment of the hypertensive patient.

While still the most difficult and most resistant form of hypertension to treat it has become apparent in recent years that even the patients with renal failure have a better outlook than ever before because of antihypertensive drug treatment. A recent study by Woods and Blythe [8] indicates that many of their patients with azotemia can live in relative comfort for years providing one is successful in controlling the blood pressure. Because hypertension appears to be the important pathogenetic mechanism in producing nephrosclerosis, it seems probable that adequate reduction of blood pressure will arrest or at least retard the further progression of the arteriolosclerotic process.

I have not had as much success in treating the uremic hypertensive patient with antihypertensive drugs alone. Particularly in the uremic patient with malignant hypertension only a moderate prolongation of life generally has been obtained, in contrast to the nonuremic patient with malignant hypertension where survivals as long as 20 years have been personally observed following antihypertensive treatment. On the other hand, several almost terminal patients with uremia secondary to malignant hypertension have had their useful lives preserved by renal transplantation, which may provide the final last-ditch hope for these most advanced cases.

It is becoming increasingly apparent that antihypertensive drug treatment represents one of the great medical triumphs of the current era. This is doubly significant in that it represents the first successful therapeutic attack on the so-called "degenerative" cardiovascular diseases of middle and old age. The value of treatment in patients with diastolic blood pressures averaging above 115 mm. Hg has been firmly established. Although definitive proof is still lacking for the treatment of the milder cases, it seems entirely reason-

able, in view of the available evidence, that reduction of the blood pressure in an early stage of the disease will prevent the complications of hypertension from developing, including many of the atherosclerotic complications. An important remaining question is, at what level of blood pressure should one begin treatment? If the life insurance statistics are heeded, perhaps treatment should be instituted at diastolic levels presently regarded as normal. However, before this is done antihypertensive drugs must be made safer, cheaper, and more easily regulable than they are today.

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