Treatment of Hypertension*

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Our ideas about the management of hypertension have changed considerably in recent years. There is now general agreement that all patients with accelerated hypertension, as manifested by high diastolic pressure and Group III and IV funduscopic changes, should have their blood pressure reduced with antihypertensive agents. Differences of opinion still exist, however, in respect to the treatment of the less rapidly advancing types of hypertension. It is apparent that the life history of untreated essential hypertension varies widely from those patients whose lives are cut short in a matter of a few years, to those who survive to old age. The problem is further complicated because antihypertensive treatment is neither simple, innocuous, or inexpensive.

If we are to approach a solution to this problem we need to know the answers to two questions. The first is: *Does antihypertensive treatment prevent the organic complications associated with hypertension?* and the second, *How can we recognize and differentiate the patient who will develop serious complications from the patient who will live out a normal span of life?*

Is Therapy of Hypertension Necessary?

Let us consider first the question of blood pressure reduction in preventing organic complications. The evidence is very good that any form of treatment which lowers blood pressure has a beneficial effect on hypertensive congestive heart failure. Cardiac failure has fallen from a major cause of death to a minor cause in adequately treated hypertensive patients. In addition, since antihypertensive treatment is effective in reversing the accelerated phase of hypertension, it follows that the transition to the accelerated phase should be prevented in adequately treated patients. There also is evidence that the incidence of cerebral hemorrhage has been reduced. Thus, it appears that antihypertensive therapy is useful in preventing congestive heart failure, accelerated hypertension, and cerebral hemorrhage.

There are as yet no reliable data to indicate whether antihypertensive treatment prevents atherosclerotic complications such as myocardial infarction and cerebral thrombosis. It is apparent that hypertension accelerates and aggravates the atherosclerotic process. Hypertension in some way predisposes the arterial walls to the deposition of atherosclerotic plaques. Atherosclerosis is commonly found in the pulmonary artery, for example, in long-standing pulmonary hypertension, and in the aorta in the region of high pressure above a coarctation. Once formed, however, it seems highly unlikely that atherosclerotic plaques could be influenced by antihypertensive treatment. In addition, we know that chronic elevation of pressure leads to structural changes in the arterial walls, including fragmentation of elastic tissue. It is possible that these irreversible structural changes provide a favorable environment for the development of atherosclerosis even after the blood pressure has been reduced. These considerations suggest that blood pressure must be lowered in the early stages of hypertension if antihypertensive treatment is to favorably influence the future course of atherosclerotic complications.

We have similar evidence that hypertension leads to the structural changes in the renal arterioles that we call nephrosclerosis. The rapidity of development, and the severity of the nephrosclerotic process, appears to depend on both a persistently high diastolic pressure and a susceptible individual. In the presence of renovascular hypertension, where a stenosis of one renal artery is present, producing a pressure drop across the narrowed segment, nephrosclerosis develops in the opposite kidney whose arterioles are exposed to the high systemic pressure. In the kidney with the pressure drop, whose arterioles are exposed to a more normal pressure, nephrosclerosis is minimal or nonexistent. If nephrosclerosis is to be prevented, this again suggests that elevated blood pressure must be lowered at a relatively early stage in the disease.

If there is a relationship between elevation of blood pressure and atherosclerosis, as well as nephrosclerosis, then it is reasonable to assume that the extent of these pathological changes will depend on both the height and the duration of the blood pressure. If the blood pressure is high for only brief periods of time, and is normal at all other times, we would *not* expect to find vascular pathology. However, if the pressure is high all of the time, both day and night, and if this persistently high pressure lasts for many months or years, then vascular pathology would be expected.

Variability of Blood Pressure Readings

Blood pressure represents a variable manifestation. It can be strongly influenced by emotion, particularly by fear and apprehension. There are some individuals who from childhood manifest transient elevations of blood pressure, associated with apprehension, who never develop a persistent eleva-

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tion of blood pressure throughout a normal life span. These individuals may, in middle and older age, exhibit pressures of 230/130 or even higher during a visit to a doctor's office or a clinic, and yet at home their blood pressure will be normal. Such hyperresponsiveness may develop in middle age, particularly in females, or in old age in both sexes, as was shown by Pickering almost 30 years ago. These individuals may show very little organic progression.

Other hypertensive patients exhibit elevation of blood pressure throughout the day, whether they are at home or hospitalized. These patients will almost all exhibit organic changes, and the rate of progression varies in general with the height of the diastolic blood pressure.

Predicting the Prognosis of Hypertension and Need for Therapy

Thus, in evaluating hypertensive patients for treatment, we should consider not only the height of the blood pressure but, more important, its persistence or duration. When we measure blood pressure only in the office or clinic we should realize that we are being presented with a mixture of populations, some of which have severe pressure elevations most of the time, some with considerably less hypertension than they exhibit in the office most of the time, and some which are not hypertensive at all but hyperreact to situations associated with apprehension.

Another way of estimating prognosis is to determine whether organic changes are already present. We should utilize the history, the funduscopic examination, the electrocardiogram, chest x-ray, and renal function tests to estimate the degree of such damage. Unfortunately, these changes do not become apparent by ordinary clinical tests until structural damage is already well advanced. As pointed out previously, if antihypertensive treatment can be expected to produce a beneficial effect in preventing nephrosclerosis and accelerated atherosclerosis, it should be given in an early stage of the disease.

It seems evident, therefore, that physicians should obtain a more accurate estimate of the average blood pressure than has been customary in the past. If the office blood pressure is not a reliable guide, then we should determine what the blood pressure is under more representative circumstances. The most representative blood pressure that is practicably obtainable is that recorded in the home, not by the physician but by the patient himself, or better yet, by a member of his family. The office nurse can easily and quickly teach such individuals how to record blood pressure, and a few manometers can be kept on hand for two-week loans. The pressure should be recorded morning and evening for two weeks in the home and the record brought to the office on the next scheduled visit. Frequently, the blood pressure readings drop immediately or over a period of days to normotensive levels. However, *the finding of a persistent diastolic elevation above 90 mm of Hg is an important criterion for instituting antihypertensive treatment.* The higher the elevation, the more intensive the treatment will be. Of course, it is important to make certain that the blood pressure is being taken accurately by having the individual record the pressure in the physician's presence at the time of the office visit.

Other useful prognostic indices, besides the estimate of the average blood pressure and the survey for organic damage, are the age, sex, and race of the patient, and the rate of progression. These factors are well known and require no emphasis.

Antihypertensive Drugs

Saluretic Agents (Thiazides); Reserpine and Hydralazine

In the patient with persistently elevated diastolic blood pressure, but with little or no signs of organic damage, treatment can begin with an oral saluretic agent. This generally is not sufficient by itself to reduce the diastolic pressure to normal. If it is not, 0.5 mg of reserpine twice daily for two weeks, followed by a maintenance dose of 0.25 mg once daily can be added; or else hydralazine (Apresoline) may be added in a dose of 25 mg two to three times daily. If the latter is not effective, the dose can be increased gradually to 50 mg three times daily.

Saluretic agents plus reserpine frequently provide an effective combination therapy in uncomplicated hypertension. The regimen also is convenient because long-acting diuretics can be combined with 0.25 mg of reserpine, to be taken only once daily.

The principal toxic effect of reserpine is mental depression. Generally, the more intelligent the patient, the greater the danger of reserpine-induced depression. Unfortunately, other alkaloids of Rauwolfia are not very effective as antihypertensive agents and, therefore, cannot be substituted. It is important when prescribing reserpine to tell the patient that if he should begin to feel unaccountably depressed or to develop sleep disturbances, such as early morning awakening, he should immediately discontinue the drug. In addition, one should strive for the lowest possible maintenance dose, which lies between 0.1 mg and 0.25 mg daily in different patients.

The serious toxicity associated with hydralazine is definitely dose dependent. The chief toxic reaction consists of a syndrome resembling disseminated lupus which rarely, if ever, occurs when the total daily dose is maintained at 150 mg or less per day. The acute side effects of hydralazine can be avoided by a few simple maneuvers. The first is to add hydralazine to the regimen of a patient already being treated with a diuretic or reserpine or both. The latter two drugs, and particularly reserpine, tend to combat or neutralize the acute hydralazine side effects which are headache, palpitation, and tachycardia. The second maneuver is to institute the drug in low and widely spaced doses, increasing gradually. For example, hydralazine can be started in a dose of 25 mg once daily, increasing in two or three days to twice daily, and after a similar interval to three times daily. It is surprising how frequently a small dose of 25 mg two or three times daily is effective in uncomplicated hypertension when it is added to the diuretics with reserpine, or to reserpine alone. The trial of hydralazine, however, should not be abandoned until the dose has

been increased to 50 mg three times daily.

Drugs in combination

The results of the large scale double-blind V.A. Cooperative Study on Antihypertensive Agents clearly showed the additive effects of these three drugs in producing a reduction of blood pressure. The combinations of reserpine and thiazides, or of hydralazine-reserpine, or hydralazine-thiazide were clearly more effective in reducing blood pressure than any of these agents used alone. The combination of all three agents was most effective, reducing the average diastolic blood pressure to below 90 mm in the patients that had been classified as having hypertension of mild and moderate severity.

In patients whose blood pressures are not controlled with any of these combinations of diuretic-reserpine and hydralazine, it is advisable first of all to make certain that you are not being misled by high office recordings. Patients whose blood pressures are well controlled at home may completely overcome the antihypertensive effects of the drugs in the office or clinic. Here again a record of home blood pressures, taken over a two week period, will go far to clarify the situation.

Since the saluretic agents are used so widely in the treatment of hypertension, it is important to consider their adverse reactions. The most common disturbance produced by thiazides is a reduction in serum potassium levels. This usually causes no difficulty unless the patient is receiving digitalis alkaloids, in which case arrhythmias frequently are induced, due to the increased activity of digitalis in the presence of a reduction in extracellular potassium concentration. Although it is customary to advise ingestion of excess potassium in this circumstance, this cannot be depended upon to raise the serum potassium level.

Another frequent side effect of thiazide administration is hyperuricemia due to inhibition of renal tubular secretion of uric acid. In azotemic patients, this frequently precipitates attacks of gout. It seldom does in non-azotemic patients. It is advisable to control the blood pressure without thiazides in patients who develop gout. However, at times the situation demands thiazide treatment. In such a case probenecid is given to combat the hyperuricemia and colchicine is administered when necessary to control symptoms.

Patients with severe renal damage and acidosis often are unable to conserve salt. If they are placed on salt restricted diets, and at the same time are given thiazides, nitrogen retention may be intensified. The administration of sodium bicarbonate or sodium lactate to such patients sometimes results in diuresis with a fall in BUN and in the degree of acidosis.

Diabetes mellitus is occasionally precipitated by thiazides. The incidence of this complication is low and it is difficult always to distinguish between spontaneous diabetes and the drug induced variety. Finally, thiazides may induce hypersensitivity reactions with skin rash and, on rare occasions, thrombocytopenic purpura.

Adrenergic Blocking Agents

If the response to a combination of diuretic plus low doses of reserpine and hydralazine truly does not control the blood pressure, the physician has the choice of using diuretics plus adrenergic blocking agents, such as methyldopa (Aldomet), guanethidine (Ismelin), or pargyline (Eutonyl).

Orthostatic hypotension poses the main problem in administering the adrenergic blocking agents. The physician should be prepared to deal with this side effect if he is to effectively treat patients with severe hypertension. The important points in managing patients undergoing treatment with the blocking drugs are these:

1) Use saluretic agents in conjunction with blocking drugs whenever possible. The former tend to smooth out the large diurnal fluctuations of blood pressure induced by the blocking agents, and to maintain a more constant antihypertensive response from one day to the next. Saluretic agents also increase the responsiveness of the blocking agents, permitting lower doses of the latter.

2) Tell the patient at the time treatment is begun that the drug lowers the blood pressure in the erect position, that it may reduce it to such a point that he feels faint, but that the dose can be adjusted so that this symptom will not be troublesome.

3) Tell the patient that, if he does develop weakness or faintness, he is to discontinue all antihypertensive medications for that day and remain in bed until the faintness disappears. If the faintness has disappeared by the next day, he is to begin again at a *slightly* lower dose of the blocking agent, specifically a decrease of 10 to 20%. If the dose is drastically reduced, the antihypertensive effect will disappear. The aim, therefore, is to find the maximum tolerable dose, and this is frequently just below the one which produces symptoms of orthostatic hypotension.

4) Tell the patient to be cautious about drinking alcohol, as the latter in conjunction with blocking drugs may induce symptomatic hypotension. Strenuous exercise also may precipitate orthostatic hypotension.

5) Doses are titrated up to the effective level. The initial dose is small, but it is increased gradually until an antihypertensive effect or symptoms of orthostatic hypotension occur.

6) Reassure the patient that if orthostatic faintness or syncope occurs, it is not as serious as it seems; that it is equivalent to an ordinary faint, and that it can be avoided by proper regulation of dosage.

7) If the patient complains of orthostatic faintness, particularly in the morning, and if the office blood pressures are still elevated without a fall on standing, it may be either that the orthostatic effect disappears in the afternoon or evening, or else that the office recordings are abnormally elevated due to apprehension. If possible, the patient should visit the office in the morning when pressures are usually the lowest. Best of all is to have twice daily recordings taken in the home by a member of the family or the patient himself. Home blood pressure recordings are an invaluable adjunct in the treatment of severe hypertensive patients whose blood pressure levels are difficult to control.

Relative Merits of Methyldopa, Guanethidine, and Pargyline

Methyldopa is well tolerated because it produces less severe orthostatic hypotension and does not usually interfere with sexual function. It also depresses renal function less than guanethidine in patients with renal failure. On the other hand, it is effective in controlling blood pressure in only about half of the patients with severe hypertension. Three to four doses per day are required as compared to only one dose per day of the other blocking agents; it occasionally produces fever and hepatitis, and it is more expensive than the other drugs. Methyldopa is begun in a dose of 250 mg three times daily, increasing as necessary to a level of 750 mg four times daily. Elevations beyond this level generally produce little additional antihypertensive effect. The most frequent side effect is drowsiness, which is usually transient, tending to disappear after a stable dose level has been maintained for several weeks.

Guanethidine or Ismelin is begun in a dose of 10 mg once daily, and is increased every week by 10 mg until orthostatic hypotension or a reduction in supine pressure appears. In hospitalized patients or in those with severe hypertension, the doses can be raised more rapidly. The maximum dose is about 200 mg daily, although most patients will exhibit an antihypertensive effect in the range of 25 to 75 mg when thiazides are given adjunctively.

Guanethidine probably lowers blood pressure in a greater percentage of patients with severe hypertension than does any other drug. Dosage also is convenient since the total daily requirement can be taken once daily in conjunction with a long-acting saluretic agent. No hypersensitivity reactions or serious organ toxicity have been observed. Because it is a potent blocking agent, it is capable of inducing profound orthostatic hypotension. Once the dose is regulated, however, patients generally are not disturbed by this side effect. Diarrhea may be troublesome and usually calls for a slight reduction in dose. Atropine-like compounds, as well as paregoric, also can be used to combat this side reaction. While under the influence of adrenergic blockade, impotence occurs because orgasm is associated with ejaculation into the urinary bladder.

Another blocking agent in current use is pargyline or Eutonyl. Effective doses vary widely from as little as 10 mg to as much as 100 mg per day. If the latter dose is ineffective, larger amounts generally will not be effective. Pargyline is a monamine oxidase inhibitor and "psychic energizer." It does produce increased alertness and drive, sometimes to the point of inducing insomnia. Severe orthostatic hypotension can occur even in low doses. The onset of this latter effect may be delayed for several weeks or longer. For this reason, the doses should be gradually elevated with increases at widely spaced intervals several weeks apart.

Patients taking monamine oxidase inhibitors may develop severe and even fatal hypertensive responses following the ingestion of processed cheese. This unusual side effect is thought to be due to tyramine which is present in cheese.

It can be seen from this brief review that all antihypertensive agents are potentially toxic. The decision to treat a given patient, therefore, should not be undertaken lightly. To the risk of toxicity must be added the inconvenience and expense involved in lifelong treatment. An assessment of the average blood pressure and the extent of organic damage already present will help in separating those patients who require no treatment, and in determining in the remainder how intensive the therapeutic program need be. The death rates from hypertension, hypertensive heart disease, and cerebral hemorrhage appear to have been strikingly reduced since the advent of antihypertensive drug treatment. Therefore, this note of caution is not meant to discourage the application of antihypertensive agents, but rather to advocate care and discrimination in their use.