DR. DOLLERY, Moderator: The symposium this afternoon is on the medical management of hypertension, and most of us would agree that this covers the great majority of cases of hypertension. We are to have three short papers and then a discussion. The first speaker is Dr. Mitchell Perry, of St. Louis, and he will speak on "Etiology and Natural History of Hypertension."

DR. PERRY: Diastolic hypertension is a common disease, but exactly how common depends on how it is defined. Although precise definitions are essential to any comprehensive treatment of either the etiology or the natural history of hypertension, I shall neglect them, since they are not vital to the several points that I want to make.

Diastolic hypertension is considered to have multiple etiologies. Neurogenic, endocrine, and renal are the adjectives frequently used to describe them; but the justification for these terms is usually scanty at best. For instance, neurogenic hypertension is often stated to be the commonest type of hypertension, yet only in a few rare situations, such as in association with a brain tumor or following bulbar poliomyelitis, is there any real reason to implicate the nervous system. Endocrine hypertension is also considered common, yet the endocrine abnormality remains ill-defined except for rare diseases like pheochromocytoma, Cushing's syndrome, and primary aldosteronism. Renal hypertension is perhaps better understood, but I shall leave the many problems of its definition and diagnosis to subsequent speakers.

Most hypertension is not associated with any of the rare definite etiologies; it is of unknown etiology, and it is called essential. I want to stress the extremely wide range of courses available to patients with untreated essential hypertension. This can be emphasized by indicating the two extremes. Those few patients who have malignant or accelerated hypertension die very quickly of their disease; moreover, their last few months of life are miserable. Only half survive 6 months after the diagnosis has been made. Very nearly all of them die because of failure of some part of their cardiovascular renal systems, and it is the kidney that usually fails first.

The situation is very different for those patients with the mildest types of hypertension, those who have only transient and not very marked elevations of diastolic pressure and who have no demonstrable cardiac or renal damage. By and large, such patients live for a long time, perhaps for 20 years on the average; moreover, they are usually well for far the largest part of this 20 years. When they finally die, they tend to die of causes unrelated to cardiovascular renal disease, such as pneumonia and the automobile. Those who succumb to their cardiovascular renal disease, succumb to conditions such as strokes and myocardial infarction. These complications are not primarily hypertensive, rather, they are arteriosclerotic.

Hypertension and arteriosclerosis represent different pathologic processes. Hypertension does not produce arteriosclerosis, but it does
augment its rate of progression. The very frequent association of the two diseases makes it difficult to separate them clinically. Effective antihypertensive therapy is now available. Whether such therapy is antiarteriosclerotic remains to be seen. At present there is no good evidence that it is. Obviously antihypertensive therapy is mandatory for a severely hypertensive patient who is almost certainly going to die of his hypertension, and in the near future. The rationale for such therapy is much less obvious in a mildly hypertensive patient who is probably going to live for decades and who is most likely to die of conditions that are unrelated to his hypertension. In fact, it seems likely that one might have to treat as many as 20 patients with very mild hypertension for an average of as long as 20 years in order to prevent a single one from dying of his hypertension.

Dr. Dollery: We now have a representative of Cleveland, Dr. Harriet Dustan, who will speak on the subject, "To Treat or Not to Treat."

Dr. Dustan: The first decade of antihypertensive drug treatment has now passed; although much experience has been gained there are two large problems that confront the clinician. The first concerns who, if not all, of the hypertensive patients should be treated and, the second, how does one measure adequately the response to treatment. It is not yet known whether the complications of hypertension result directly from elevated arterial pressure. The reversal of malignant hypertension by antihypertensive drugs suggests that arteriolar disease is, in some way, a result of hypertension; a causal relationship between elevated blood pressure and atherosclerosis, the major complication of essential hypertension, has similarly been suggested. The Framingham study has shown an increased frequency of heart attacks in hypertensive patients as compared to normotensive patients and actuarial statistics reveal that hypertension, even of mild degree, shortens life span.

Evidence relating complications of hypertension to elevated arterial pressure, although not necessarily incontrovertible, is impressive. If it is taken at face value, the goals of treatment then become (1) to lower supine diastolic arterial pressure to normal levels or as near normal levels as possible, (2) to control or prevent arteriolar disease, and (3) to prevent development or slow progress of atherosclerosis.

If vascular disease is caused by hypertension then all patients should be treated. However, at the present time, successful therapy is not feasible for everyone because simple regimens are not effective in all patients and all treatments require relatively close supervision. Clearly, vigorous antihypertensive drug treatment should be used in patients immediately threatened by complications of hypertension, i.e., those with the malignant syndrome, heart failure, nephrosclerosis, or complications of atherosclerosis. Further, arterial pressure reduction is indicated in men with sustained diastolic hypertension, particularly those with a family history of premature death or disability from vascular disease, and in the sudden hypertensions that accompany toxemia of pregnancy or acute glomerulonephritis in children.

Experience has shown that in these patients antihypertensive drug treatments can be lifesaving; but it has not shown those in whom drugs will be unnecessary. The goal of long-term treatment of the asymptomatic hypertensive patient is the prevention of symptoms that are statistically, though not actually, inevitable. At the present time there is no way of knowing whether symptoms can be prevented. Although the patient with mild diastolic hypertension may well benefit from long-term arterial pressure reduction, this benefit is not certain enough, without longer years of experience, to warrant treatment regardless of the side effects produced. Simple, effective, and safe treatment seems not to be contraindicated in any patient; but treatments difficult to administer and difficult to take should be reserved for patients who need to have blood pressure lowered.

The second important consideration of

Circulation, Volume XXVIII, October 1963
treatment is judging the response to drugs. This is not difficult in the patient whose arterial pressure becomes normal during treatment and remains so regardless of the situation in which the measurement is made. Unfortunately, this patient is unusual. Many hypertensive patients retain a labile arterial pressure that can rise to high levels during a visit to the doctor's office. To obtain more information about response to drugs we have utilized daily home measurements of blood pressure. This procedure permits more frequent sampling of arterial pressure fluctuations than that obtained with office measurements only. However, the response to antihypertensive drugs is still difficult to analyze in the patients who have normal levels at home but high ones in the doctor's office. In short, home readings have given us more information but have not solved the problem of evaluating response.

This problem is of much more than casual importance. If a relationship between hypertension and vascular disease is to be investigated sensibly, a reliable method for judging response to antihypertensive drugs must be developed.

DR. DOLLERY: Thank you, Dr. Dustan, for that nice talk. I think Dr. Dustan escaped before she told us whom not to treat, although she told us whom to treat. Perhaps in the panel discussion later, we can find out more about that.

And now the last speaker is Dr. Richard Lyons, of Syracuse, New York, who will speak on the challenging topic of "The Use and Abuse of Drugs."

DR. LYONS: To follow Dr. Dustan's very sensible comments with another almost identical topic, "The Use and Abuse of Drugs," is superfluous. It is obvious that the major abuse of drugs is to treat when we should not treat. I was particularly startled some years ago when I was asked to see an 84-year-old lady who was being treated for hypertension. The poor lady had a blood pressure of 180/110 before treatment, and as a result of antihypertensive treatment she was completely bedridden, and all she wanted to do, of all things, was go to Atlantic City. As soon as we stopped treating her, she was able to achieve her desire, went to Atlantic City, and lived for the next 4 or 5 years very happily. She died of some other cause, as Dr. Perry has suggested. This was obviously a flagrant abuse of drugs.

It is almost unfortunate in some respects that we have so many potent drugs that will effectively lower blood pressure. We also have very potent drugs to rid the body of sodium, but this is perhaps a little less unfortunate. For nearly 60 years, it has been known that if a patient avoided salt, and was maintained on a very low salt regime, the blood pressure would generally decrease. Amberg pointed this out in 1904. Dr. Allen, I think, in 1922, was very vigorously proposing this regime, and, more recently, Dr. Kempner and others have clearly shown that if we can take salt away from people, we can help them. Now the chlorothiazide compounds may do the same thing and allow us to have a reasonable diet. This is perhaps not an abuse in any way and it at least allows the patient to survive with a reasonably decent life.

When it comes to some of the other drugs, however, one must remember that they are all toxic for certain people. Even simple things such as reserpine have produced profound depressions in certain individuals and any variation of the reserpine compounds may produce profound depression. Although a careful physician would very seldom, if ever, give a patient digitalis without following him carefully, unfortunately patients are often given potent antihypertensive drugs without the same careful follow-up. This is clearly an abuse. In the same way, if we use any of the antihypertensive drugs in inadequate amounts, we are doing almost no good whatsoever. As Dr. Perry has already pointed out, it is very seldom that we get a patient with hypertension who has not been treated with one thing or another. But commonly the treatment has been almost homeopathic, and perhaps this is just as well. In any event, it has not produced the pharmacologic effects that we would be looking for and, therefore,
in my mind, is an equal abuse of drugs.

I always used to believe that it was proper to approach this problem with the following statement: When the patient has malignant hypertension, the doctor has a right to be malignant and to use basically all drugs at his command in full force; but in benign hypertension the doctor should be benign. Perhaps this might be modified slightly by the work of Dr. Dollery's former countryman, Dr. Smirk, who has indicated that he has prolonged the lives of those people whom he thought had grade-II hypertensive disease, a rather benign disease. He believes that he has not only increased the life span but also decreased the amount of cardiac enlargement, renal involvement, and vascular involvement. Certainly, any patient who is deteriorating from vascular disease, I think, deserves treatment and might be classified as semimalignant.

**Dr. Dollery:** We now have about 20 minutes for discussion and I want to put some specific questions to the speakers. I am going to ask them to keep their answers short. My first question is, if you have a male patient, aged 48 years, with a blood pressure of about 170/110 (both office readings and home readings), but without any complications or symptoms, would you treat or not treat?

**Dr. Dustan:** Yes, I would.

**Dr. Lyons:** I am not so sure I would. If his diastolic pressure was consistently 110 or lower, and he was feeling well and having no vascular disease, I might advise him to take long weekends.

**Dr. Dollery:** Sounds like good advice.

**Dr. Perry:** I would treat such an individual, and I would treat him sufficiently to lower his pressure. I would use 110 mm. Hg as the dividing line. If the average diastolic pressure at hospital rest were lower than this, I would not treat.

**Dr. Dollery:** Well, obviously I chose this value to be near the dividing line. We have had a majority of the panel say they would treat this patient.

**Dr. Dustan:** May I modify my statement? I would treat this person, Dr. Dollery, if this could be done well. If this were a person who, for one reason or another, could not be easily treated, I would not struggle with it. I would try but, if treatment were difficult, I would desist. I would not treat this patient at all costs.

**Dr. Dollery:** If this patient lived across the street from the Cleveland Clinic, you would treat him.

**Dr. Dustan:** Yes, if he were intelligent, were interested in cooperating, and would take his own blood pressure.

**Dr. Dollery:** Have you any evidence that treating this patient with antihypertensive drugs would help him?

**Dr. Dustan:** No, I have no evidence for this particular individual, nor do I know how to get it, but the Framingham experience and the actuarial statistics suggest that the sustained hypertension may be harmful.

**Dr. Dollery:** I think we would all agree that actuarial statistics show that even a very mild elevation of the blood pressure, even 150/85, has been shown by the life insurance companies to be associated with a significantly increased mortality. The vital question is whether or not we can influence this. Dr. Perry, do you have any evidence?

**Dr. Perry:** No, I do not have the slightest evidence. I would not treat such mild disease until this sort of evidence is available, and it is going to be very difficult to obtain.

**Dr. Dollery:** Dr. Lyons referred to Dr. Smirk's work in New Zealand and many of you are familiar with it. It is generally agreed in malignant hypertension and in patients with exudative retinopathy that the bad outlook is improved by treatment. Some of us are critical of Dr. Smirk's conclusions in mild disease because his control (untreated) group were mostly patients who for some reason defaulted from treatment. This is not a proper control group and the evidence is not really adequate.

The next question is the general question of the safety of the drugs that we use. This is a very important issue indeed at the present time. Those of us who treat hypertension are carrying on the biggest long-term chronic
toxicity study that has ever been undertaken. We must be very careful in what we do and the drugs we choose. I want to talk a little about the thiazide diuretics because I think in most clinics and for most people treating hypertension, this is the main “background” therapy now used. These diuretics cause sodium and potassium depletion but they also cause elevation of uric acid and they sometimes cause hyperglycemia. Are we running into trouble from the long-term chronic use of thiazide diuretics?

Dr. Lyons, do you use thiazide diuretics a great deal and are there any special precautions you take in patients who are having these drugs?

Dr. Lyons: I always worry about the development of gout, both in males and females. I am frankly not worried about losing calcium. I think we will have had harbingers of this long before serious calcium loss, in terms of renal stones and other things.

Dr. Dollery: Dr. Perry, how do you feel about this?

Dr. Perry: I am not particularly worried about producing gout or uncovering latent diabetes. These seem to be reversible phenomena. My major objection to the promiscuous use of thiazides is the greatly increased risk of digitalis toxicity in a potassium-depleted patient. We may not be making the critical measurement to uncover a presently unsuspected toxic effect that may be very slow and subtle in manifesting itself.

Dr. Dollery: I think there is another objection too, in that if you have long-term potassium depletion, in laboratory animals, these animals get renal tubular damage and may develop pyelonephritis.

We have been particularly concerned about the problem of diabetes. This was not with the thiazides commonly used in clinical medicine, but with the drug diazoxide, which is a nondiuretic thiazide. On this drug two patients became acutely diabetic. One of these patients had a normal glucose tolerance curve before treatment. Both of these patients got better. In one, we measured the plasma insulin and found that it was low, so it is the pancreatic islet cells that are damaged.

Dr. Dustan, do you routinely measure uric acid; do you routinely measure blood sugar or do you test the urine for sugar; should we all be doing this if we have patients on these diuretic substances?

Dr. Dustan: Yes, we routinely measure blood uric acid and blood sugar levels as well as levels of plasma sodium, potassium, carbon dioxide, and chloride. How often these measurements should be made I don’t know. It is my understanding that gout and diabetes appear during thiazide diuretic treatment in people who have a basic potential for developing these abnormalities. Because of this, the appropriate measurements should be made before treatment is started and at yearly, or more frequent, intervals thereafter.

Dr. Dollery: Do you measure glucose tolerance curves before you start treatment with thiazide diuretics?

Dr. Dustan: No.

Dr. Dollery: Now, I would like to move on to the next question and this is the question of vascular disease in hypertension. It is now uncommon for hypertensive patients to die from heart failure unless they, for example, get myocardial infarction. Whereas in the old days, many patients died from heart failure, patients nowadays die from vascular complications of hypertension. The question is, are we affecting the vascular disease? Firstly, can we expect any regression of existing vascular disease when we treat hypertension, and the second question is, can we prevent further progression? These are mutually exclusive questions and I would like to ask Dr. Perry for his view.

Dr. Perry: I do not know of any good data that pertain to relatively mild hypertension. We do have some interesting preliminary data on the effects of protracted treatment in severe hypertension (fig. 1). These data compare the survival rates of patients with malignant hypertension (characterized by hemorrhagic and exudative retinitis with papilledema), on the one hand, and severe benign hypertension (Smithwick’s grade IV), on the other. Initially the malignant hyper-
tensive patients did less well, but eventually they did better. The figure indicates that during the first 3 years of therapy the malignant hypertensive subject had a lower survival rate. From 3 to 5 years, the survival rates of the two groups were comparable. From 5 to 10 years, the malignant hypertensive subjects had a higher survival rate. Patients with malignant hypertension not only tended to die early, but they also tended to die of renal failure. In contrast, those with severe benign hypertension died at an almost constant rate, and they died primarily of arteriosclerotic complications, particularly thrombotic strokes.

**Dr. Dollery:** Is this because of a different age composition of these two groups?

**Dr. Perry:** There was some difference in age composition. The malignant hypertensive patients averaged 45 and the severe benign hypertensive patients 49 years of age. I doubt that the differences in survival can be explained on this basis.

**Dr. Dollery:** Dr. Lyons, do you feel that we are influencing vascular disease and benign hypertension by our treatment?

**Dr. Lyons:** If you would like to define benign hypertension as an accelerated benign hypertension; in other words, we quibble between what Dr. Perry is calling malignant hypertension and I will say benign hyperten-

sion with vascular breakdown. In certain people who are beginning to have vascular breakdown I believe that the rate and intensity of the vascular breakdown may be checked as you treat vigorously. In other words, when we see fresh hemorrhages in the eyegrounds, some increase in level of blood pressure and new albuminuria, vigorous treatment, rest in bed, and other drugs may prevent the new hemorrhage and decrease the albuminuria as well as lower the pressure.

**Dr. Dollery:** This is pretty severe hypertension, when there are hemorrhages in the eyegrounds and albuminuria. Do you think you are influencing the vascular disease in patients with less severe but still high pressures?

**Dr. Lyons:** The only data that we really have are those of Smirk, and I would agree with your criticism.

**Dr. Dollery:** Dr. Dustan, what do you think about this, because this is really one of the critical issues, isn't it?

**Dr. Dustan:** It is a critical issue but has two aspects, I believe. One is the effect of blood pressure reduction on arteriolar disease, such as occurs in malignant hypertension, and the other is the effect on atherosclerosis, the chief complication of essential hypertension. If blood pressure control were not important in affecting arteriolar disease, this should develop in people under treatment. As yet we have not seen this when treatment was adequate. The other aspect, the prevention or slowing of atherosclerosis by arterial pressure reduction is presently impossible to measure. Further, it seems far too soon even to judge unless the information which Dr. Perry has is clear enough to show this.

**Dr. Lyons:** When we have the answer to aging, none of us will need to be up here.

**Dr. Dollery:** I think this is not just a matter of the aging process, is it? If the vessel changes in hypertension were purely spasm of vascular smooth muscle then the problem would be an easy one, which we might hope to reverse. But the problem, in fact, is structural change in vessel walls, and it has always seemed to me that we are un-
likely to be able to reverse these structural changes and some data we have collected by serial photography of the retina are in support of this. Even when you lower the blood pressure with drugs extremely efficiently or even cure it by arterial surgery in the kidney, the results in the eye grounds are practically none at all. The narrow segments stay narrow and the vessels stay narrow, so this is rather disappointing. I think the best, perhaps, that we can hope for from this sort of treatment is that we slow the further development of vascular disease and that in itself is important.

Now I want to shift on to the question of drugs.

Dr. Dustan, what is your drug of first choice? My own feeling about reserpine is that although it is a useful drug, the number of people who get a really big reduction in pressure with this is quite small.

Dr. Dustan: I would tend to oppose your feeling. Dr. Dollery, about the usefulness of reserpine. I would probably start the patient on an oral diuretic. While the antihypertensive effects of reserpine and oral diuretics may not be equal, these are drugs that have few serious side effects.

Dr. Dollery: I would like to ask the panellists if they have any experience with methyl-dopa, because this is the only major new drug that has been introduced into antihypertensive therapy during the last 2 years.

Dr. Lyons, have you any experience with this drug?

Dr. Lyons: A rather limited amount. I found it a very useful drug except for the amount of drowsiness that one gets at first. Many of these people will get over the drowsiness but at first I was a bit alarmed at putting people to sleep so easily.

Dr. Dollery: And what do you consider the particular advantages of this drug, or aren't there any?

Dr. Lyons: Except for the drowsiness, I found it had relatively little side effects. It does lower the blood pressure to a modest degree, not too violently, such as one would see with blocking agents.

Dr. Dollery: We have found that this drug methyl-dopa (I have treated nearly 100 patients with it) does seem to lower the recumbent pressure more than guanethidine would, for example. This is a real advantage although there is considerable individual variation in the amount of the postural effect. Do you agree with this, Dr. Perry?

Dr. Perry: Yes, I would agree. My criticisms of methyl-dopa are that it has only a modest effect and that tolerance develops to it. In this connection, I would like to emphasize that impotent regimens may have very real dangers. In St. Louis, we are intrigued by the disappearance of classical malignant hypertension among apparently untreated patients. Table 1 suggests that although the frequency of severe hypertension has not changed, it now presents in a different manner. The typical, severely hypertensive patient of 10 years ago entered with ambyopia and marked changes in his ocular fundi but relatively uncompromised kidneys. He has been replaced by a patient with nearly normal fundi but with failing kidneys.

This change in the pattern of apparently untreated hypertension is distressing, since severe hypertension can be treated much more satisfactorily before renal failure appears. It seems likely that many apparently untreated patients received small doses of oral diuretics or rauwolfia alkaloids. This might have protected their ocular fundi, which are known to be very responsive to any diminution in blood pressure, but might have failed to pro-

Table 1

<table>
<thead>
<tr>
<th>Years</th>
<th>No. of patients</th>
<th>Per cent with hemorrhagic retinits</th>
<th>Per cent with azotemia</th>
<th>Per cent with hemorrhagic and azotemia</th>
</tr>
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<tbody>
<tr>
<td>1950-52</td>
<td>27</td>
<td>48</td>
<td>4</td>
<td>48</td>
</tr>
<tr>
<td>1958-60</td>
<td>27</td>
<td>15</td>
<td>30</td>
<td>56</td>
</tr>
</tbody>
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During the earlier period neither rauwolfia alkaloids nor oral diuretics were available, whereas during the later period it was difficult for hypertensive patients to avoid them.

Circulation, Volume XXVIII, October 1968
tect the kidneys, where damage is notoriously irreversible.

Dr. Dollery: We are very nearly at the end of our hour, so I intend to say just a few words to summarize what our speakers have said. It is clear that the real problem in the treatment of hypertension is what to do about the mild and moderately severe cases. We have all agreed that malignant hypertension, accelerated hypertension of any form, has to be treated. But the problem of these relatively mild cases is a very great one because of two factors. Firstly, the stamina that is required from both the patient and the physician and, secondly, because we do not really know whether we are going to do these patients any good. There is room for much further work here over a very long time. If we want to know whether a patient such as I chose as an example—a man with a blood pressure of 170/110 at the age of 48—is going to be benefited by treatment, we may have to follow large groups of patients for more than 20 years. Most of us who are engaged in clinical therapeutic research are not accustomed to thinking in such long time spans. It has got to be a cooperative effort because it is unlikely that any one man is going to have sufficient patients. The only study that I know of is going on in this area is the Veterans Administration study run by Dr. Freis, but this does have a drawback that is almost confined to male patients, whereas about two thirds of hypertensive patients are women. The second problem is in the selection of drugs. Although we all may have our favorite drugs, nevertheless we all have to admit that each of these drugs has substantial disadvantages. We can say one thing firmly to the pharmacologists who are interested in developing new drugs and that is that we have no further use for drugs that lower the blood pressure much more in the standing position than in other body positions. These drugs undoubtedly help to keep alive many people who would otherwise have died of malignant hypertension, but we now need drugs that will control the blood pressure in all positions and at all times of day.

With those few words I will finish and thank the speakers on your behalf for this discussion.

Cardiology

It was not until the eighteenth century, with the publication of observations on morbid anatomy made by Raymond Vieussens (1715), Lancisi (1718, 1740), and Morgagni (1761), and the first treatise dealing specially with diseases of the heart by J. B. de Senac (1749), that cardiac disease was really recognized. Theophilus Bonetus (1620-89), in the first volume of his Sepulchretum (1679), collected a number of observations on palpitation and cardiac pain during life associated with polypi in the heart, calculi in the myocardium, inflammation of the heart, acute inflammation, effusion and adhesion of the pericardium, and aortic aneurysm, and thus prepared the way for Morgagni and others. Sir Humphry Davy Rolleston. The Harveian Oration. Great Britain, Cambridge University Press, 1928, p. 13.
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