OVER the past 10 years a steadily increasing number of asymptomatic people with diastolic blood pressures between 90 and 100 mm Hg have been treated with antihypertensive drugs, more in the United States than anywhere else in the world. The expanding treatment of these 20 to 25 million people unquestionably represents the most extensive use of drugs ever attempted for the prevention of disease. As a result, in the United States the treatment of mild hypertension is now the leading indication for visits to physicians' offices and the use of prescription drugs.

Many physicians argue that this steadily expanding use of drugs to treat milder and milder degrees of hypertension is necessary and has already proved to be valuable in saving lives and preventing disability. They point to data showing a progressive and substantial decline in cardiovascular mortality since 1968 as a beneficial consequence of this practice. A smaller number of physicians have questioned the wisdom of this push toward drug therapy. In the words of the English epidemiologist Geoffrey Rose:

"We may be unable to identify that small level of harm to individuals from long-term intervention that would be sufficient to make that line of prevention unprofitable or even harmful. Consequently we cannot accept long-term mass preventive medication."

In his analysis, Dr. Rose used the clofibrate experience as an example of the unforeseen hazards of long-term preventive medication. His admonition has been strengthened by the recently published final report of this trial, which documents an 11% higher mortality in the clofibrate-treated group attributed to a wide variety of causes other than ischemic heart disease.

We believe that similar though less obvious hazards have surfaced in the clinical trials of the therapy of mild hypertension. We also believe that the ethical justifications for the use of drugs to treat mild hypertension have not been completely fulfilled. As delineated by Brett, three links of evidence are needed to justify risk factor intervention: (1) the epidemiologic evidence that a factor confers risk, (2) the availability of a therapeutic modality that changes the numerical expression of the factor, and (3) the evidence that such a numerical change leads to improved outcome.

For mild hypertension the first two of these links have been provided. In regard to the first link, however, we should remember that the degree of risk for most persons with mild hypertension is relatively small and that those who are at higher risk can be identified reasonably well. It is the third link — the evidence for an improved outcome — that remains in doubt. We would also add a fourth necessary link to justify preventive intervention: the absence of substantial side effects that interfere with the quality of life. We will come back to this issue after we examine the evidence for an
improved outcome resulting from the reduction of blood pressure by use of antihyper-
tensive drug therapy.

Evidence from Therapeutic Trials That Therapy Improves Outcome

The evidence that therapy improves outcome was provided in 1967 for patients with severe hypertension (i.e., diastolic blood pressure >115 mm Hg) and in 1970 for patients with moderate hypertension (i.e., diastolic blood pressure > 104 mm Hg). Thereafter, most clinicians made what appears to be a logical assumption: what was good for patients with severe and moderate hypertension would also be good for those with mild hypertension. Fortunately, trials were begun in the early 1970s to determine if such therapy did, in fact, improve outcome by preventing cardiovascular disease among patients with mild hypertension. Four trials have been completed, and a fifth, the English Medical Research Council trial, is near completion. Because the Veterans Administration Cooperative Study Group and the U.S. Public Health Service Hospitals Cooperative Study Group included patients with diastolic blood pressures from 90 up to 115 mm Hg (i.e., both mild and moderate hypertension), these trials are not included in our discussion.

The results of these four studies show some protection (Table 1). In the Australian and Oslo trials, which compared a nontreated control group with a drug-treated group, overall mortality was only reduced from 28 to 19 patients and coronary mortality was only reduced from 10 to 8 patients. When the difference in total mortality, 9, is divided into the number of patients in each group, 2100, the figures show that 1 death was averted for every 233 people treated for 3 to 7 years.

Because the Hypertension Detection and Follow-up Program (HDFP) and the Multiple Risk Factor Intervention Trial (MRFIT), both done in the United States (Table 1), enrolled patients with blood pressure levels across the entire range of high blood pressure, it was considered unethical to deny therapy to the half of patients. Therefore, half the subjects were given more intensive, special care and were compared with the other half, who were given less intensive, usual care. Because most subjects in both groups were treated, neither study can be considered to be an unambiguous trial of the effect of antihypertensive drug therapy. Less mortality — total and coronary — was observed in the more intensely treated half of the HDFP population, but no protection was found in the MRFIT patients who were given more therapy.

If the results of all of these trials are combined, admittedly a statistically suspect thing to do, the protection shown by therapy or more intense therapy for 3 to 7 years would be one death from all causes per 156 people and one death from coronary disease per 455 people. We should remember that a statistically significant reduction in total and coronary mortality has been demonstrated in only one of the four trials, the HDFP. In the Oslo trial and in the portion of the MRFIT population who had an abnormal electrocardiogram on entry, more coronary deaths occurred in the treated or more intensely treated groups.

| Study            | Blood pressure range (mm Hg) | No. of patients | Total mortality | Coronary mortality |
|------------------|------------------------------|-----------------|-----------------|-------------------|-------------------|
|                  |                               |                 | Control | Treated | Control | Treated | Control | Treated | Control | Treated | Control | Treated | Control | Treated | Control | Treated | Control | Treated | Control | Treated | Control | Treated | Control | Treated | Control | Treated | Control | Treated | Control | Treated | Control | Treated | Control | Treated | Control | Treated | Control | Treated |
| Drugs versus placebo | 95–109                        | 3427            | 19     | 9      | 8       | 2      | 19      | 9      | 8       | 2      | 96      | 91      | 96      | 91      | 96      | 91      | 96      | 91      | 96      | 91      |
| Australian15     | 90–109                        | 785             | 9      | 10     | 2       | 6      | 19      | 9      | 8       | 2      | 96      | 91      | 96      | 91      | 96      | 91      | 96      | 91      | 96      | 91      |
| Oslo16           | 90–109                        | 4212            | 28     | 19     | 10      | 8      | 19      | 9      | 8       | 2      | 96      | 91      | 96      | 91      | 96      | 91      | 96      | 91      | 96      | 91      |
| Subtotal         |                              |                 | 20,049 | 196    | 174     | 196    | 174     | 196    | 174     | 196    | 174     | 196     | 174     | 196     | 174     | 196     | 174     | 196     | 174     |
| More versus less treatment | 90–104                      | 7825            | 291    | 231    | 107     | 86     | 460    | 405    | 186     | 166    | 460     | 405     | 186     | 166     | 460     | 405     | 186     | 166     | 460     | 405     | 186     | 166     |
| HDFP17           | 90–115                        | 8012            | 169    | 174    | 79      | 80     | 169    | 174    | 79      | 80     | 169     | 174     | 79      | 80      | 169     | 174     | 79      | 80      | 169     | 174     |
| MRFFIT18         |                              |                 | 15,837 | 460    | 405     | 186     | 166    | 460    | 405    | 186     | 166    | 460     | 405     | 186     | 166     | 460     | 405     | 186     | 166     |
| Subtotal         |                              |                 | 20,049 | 196    | 174     | 196     | 174    | 196    | 174    | 196     | 174    | 196     | 174     | 196     | 174     | 196     | 174     | 196     | 174     |

HDFP = Hypertension Detection and Follow-up Program; MRFIT = Multiple Risk Factor Intervention Trial.
The inability to document clearly an improved outcome may reflect the mode of therapy used in the trials; blood pressures that are naturally lower are associated with less cardiovascular disease. In all of the trials shown in the table diuretics were used as the first and often the only drug, often in high doses that frequently induced hypokalemia. The possibility exists that diuretic-induced hypokalemia could have precipitated the arrhythmias responsible for the excess sudden deaths seen in the Oslo and in a portion of the MRFIT populations.

Even the small amount of protection shown in the overall data from the four trials could well be accepted as proof of a need for therapy if we could ensure that, in Dr. Rose's words, "there was 'no small level of harm to individuals from long-term intervention.'" Such harm may, in fact, have been shown in the two trials comparing the effect of drugs with that of placebo. In the Oslo trial, higher morbidity and mortality were noted among the treated subjects. In the Australian trial, total end points (morbidity and mortality) were higher at each level of blood pressure below 100 mm Hg among those patients receiving drugs than among those receiving a placebo (Figure 1).

We simply cannot be sure that the therapy of mild hypertension, as it has been provided, has not induced a certain level of harm at the same time that it has reduced the risks of an elevated blood pressure. In an analysis of data from England, Bulpitt concluded that treated hypertensive subjects under the age of 50 years still had a fourfold increase in mortality compared with the general population, whereas this excess death rate was not seen among older men receiving antihypertensive therapy. Similarly, the incidence of coronary heart disease remained higher than that predicted by posttreatment blood pressure levels among a small group of patients treated for 6 years. Moreover, among 7610 Japanese men in Hawaii, those who initially received antihypertensive therapy had a higher subsequent 10-year mortality from cardiovascular diseases, including heart attacks and strokes, as compared with untreated men at every level of blood pressure. Although the authors of this study assume that this "apparently paradoxical finding probably reflects more advanced status of hypertension existing before treatment rather than adverse effects of drugs per se," they add that "this latter possibility cannot be dismissed."

Regardless of these suggestive reports, the available data are too limited to answer the question of whether therapy that reduces the blood pressure also reduces the risks to the level of the posttreatment blood pressure. If not, as suggested by these limited data, the hazards of therapy may add their own risks. On the other hand, the cardiovascular damage induced by hypertension, once developed, may never totally disappear despite long-term maintenance of a normal blood pressure. In the latter scenario, higher posttreatment risks should not be blamed on the therapy.
Evidence of a Role for Hypertension Control in Reducing Cardiovascular Mortality

Even though the evidence from the therapeutic trials is not conclusive, one could argue that the more widespread therapy of hypertension seen over the past 10 to 20 years has been a major factor in the steadily falling death rates from heart attacks and strokes since 1968. As plausible as this seems, the evidence is not at all solid. First, we are not sure of the contribution of all preventive measures, including treatment of hypertension, as reflected in a reduced incidence of new cardiovascular disease events (i.e., primary prevention) compared with the role of therapy after the event (i.e., secondary prevention). There is evidence for a lower incidence that supports a role for primary prevention, but in the study of the Minneapolis–St. Paul area from 1970 to 1980 the largest decline occurred in patient fatality in the hospital rather than in the rates of hospitalization for coronary heart disease. Second, if primary prevention plays a substantial role, the relative contribution of the control of hypertension is unknown. Its effect should be particularly obvious in a decline in the incidence of stroke, which is considered to be more purely "pressure-related" than other cardiovascular diseases. The incidence of stroke began to fall among the residents of Olmstead County, Minnesota, in the early 1950s, however, long before the availability of antihypertensive therapy for any but a handful of severely hypertensive subjects. Analysis of all available data suggests that the cessation of smoking has played the major role in the decline of overall mortality caused by cardiovascular disease, with a lesser role for reduction of both lipids and blood pressure.

The MRFFIT data also raise doubts about the role of antihypertensive therapy. As noted in the table, the use of more intensive therapy for hypertension did not result in lower mortality, either total or coronary. Protection was obtained by the reduction in cigarette smoking among those who smoked and by lowering serum cholesterol levels among those who were hypercholesterolemic. Parenthetically, the improvement in overall and cardiovascular mortality since 1968 could, at least in part, reflect the greater access to health care provided to the indigent and elderly by Medicare and Medicaid, which were introduced in 1965. Recent cutbacks in such programs have been shown to adversely affect health, specifically the level of blood pressure control. Whatever else we do, we should not lose sight of the higher prevalence and severity of hypertension among the indigent and the elderly and of the need to ensure that their access to health care is not curtailed further.

The Fourth Link: Quality of Life

The need to add this fourth link is stated well by Brett:

When proposing drug therapy, the physician cannot make an asymptomatic person feel any better, but might make him feel worse, since most drugs have some incidence of adverse effects. But how should side effects be quantitated on a balance sheet of net drug benefit? If a successful antihypertensive drug causes impotence in a patient, how many months or years of potentially increased survival make that side effect acceptable? There is obviously no dogmatic answer; accordingly, global statements such as "all patients with asymptomatic mild hypertension should be treated" are inappropriate, even if treatment were clearly shown to lower morbidity or mortality rates.

Unfortunately, none of the trials shown in the table even attempted to measure the effects of therapy on the quality of life or on functional capacity. But side effects did occur. In the HDFP trial, for example, more than a third of the patients receiving more intensive therapy experienced an adverse reaction. In the ongoing Medical Research Council of England trial, almost 20% of patients taking either a diuretic or a β-blocker withdrew from therapy because of side effects. The prevalence of impotence increased from 10% among those receiving a placebo to 13% among those receiving a β-blocker and to 22% among those receiving a diuretic.

The Need for Flexibility

All things considered, the decision to use drug therapy should not be based on dogmatic rules and rigid numerical criteria. We agree with Guttmacher and colleagues, who found that the selection of the level of blood pressure that is deemed in need of therapy reflects a value judgment as to when the risk is considered serious enough to justify treatment. As stated by Brett, "The reasons to intervene should be viewed as gradually more compelling as blood pressure rises, rather than suddenly compelling at a specific level such as 90 mm Hg."
We need better indices of risk to sharpen our ability to select those persons in need of therapy. Currently, we cannot predict coronary heart disease with great accuracy. Among men placed in the top 15% of risk based on age, smoking habit, and levels of blood pressure and cholesterol, overt coronary heart disease developed in only 7% over the subsequent 5 years.33

We believe that better indices of the risks of mild hypertension will become apparent and available. For example, the presence of echocardiographic evidence of left ventricular hypertrophy may serve as a better marker of risk, although it may prove to be too sensitive. In addition, the ambulatory blood pressure obtained over 24 hours has been shown to be more accurate than occasional office readings in the prediction of cardiovascular morbidity and mortality.34

Beyond the differences in risk, patients may vary in how much benefit they derive from the treatment of high blood pressure. In the Australian trial,35 complications among the placebo groups were more likely in those who were older, had higher systolic pressure, were smokers, and were underweight. Treatment was most beneficial in underweight smokers and in those subjects who started with a lower systolic pressure or lower serum cholesterol levels. Thus, neither the risks nor the benefits can be assumed to be uniform in all patients with a given level of blood pressure.

The acceptance of the belief that therapy must be viewed as a balance between risk and benefit should result in a more cautious, conservative use of drug therapy. However, the same approach may mandate even more aggressive use of drugs in some patients, such as hypertensive diabetics with any evidence of renal damage. The poor prognosis of such patients if left untreated and the evidence that reduction of their hypertension will slow the inexorable progress of renal damage36 can be taken as justification for therapy in those with diastolic levels well below 90 mm Hg.

The Problem of Labeling

Beyond the need for flexibility and individuality in deciding on the need for drug therapy, there is another reason to take our time in dealing with the majority of patients with mild hypertension. In all of the therapeutic trials and other studies wherein multiple blood pressures have been taken, most patients have a reduction in their initially high blood pressure, at least over a 3- to 4-month period. As many as a third of those subjects initially found to have a diastolic blood pressure above 95 mm Hg in the HDFP screening program had a diastolic blood pressure below 90 mm Hg on a subsequent examination.17 In the Australian trial, 48% of those subjects receiving a placebo whose initial diastolic blood pressure (the mean of four readings) was between 95 and 109 mm Hg had a reduction in their average diastolic blood pressure to below 95 mm Hg during the next 3 years.37 The 3 to 4 months wherein most of the nonspecific decline in blood pressure occurs, if it is to occur, can be used to apply those nondrug therapies that are without risk and of potential benefit in treating hypertension.38

The incorrect labeling of a person as hypertensive may result in psychiatric morbidity and disability as reflected in chronic absence from work.40 If the newly labeled patient is provided active follow-up and treatment, these adverse effects appear to be overcome. Care is obviously needed, not only in the decision to treat but also in the identification of a person as hypertensive.

Regardless of the reservations expressed in this editorial, we should not lose sight of the protection against cardiovascular diseases that has been documented by reduction of the blood pressure with antihypertensive drug therapy in persons with moderate and severe degrees of hypertension. But such patients comprise only about 20% of the hypertensive population. It is among the other 80% — those with mild hypertension — that therapy has been assumed to be of value and is being applied in rapidly increasing amounts to a rapidly expanding population. We believe that it is possible to overuse drug therapy and that a more cautious approach to mild hypertension is warranted.

References

14. Veterans Administration Cooperative Study Group on Antihypertensive Agents. Effects of treatment on morbidity in hypertension. II. Results in patients with diastolic blood pressure averaging 90 through 114 mm Hg. JAMA 1970;213:1143-1152
17. Hypertension Detection and Follow-up Program Cooperative Group. Five-year findings of the hypertension detection and follow-up program. I. Reduction in mortality of persons with high blood pressure, including mild hypertension. JAMA 1979;242:2562-2571
31. Caru J, Borhani NO, Blaszkowski T, Fotiu S, Zimbaldi N. Adverse reactions to antihypertensive drugs in the hypertension detection and follow-up program (HDFP) [Abstract]. Circulation 1982;66(suppl II):II-328

Address for reprints: Dr. Norman Kaplan, Department of Internal Medicine, University of Texas Health Science Center, Southwestern Medical School, Dallas, Texas.