The Medical Research Council Trial

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THE medical literature over the past half dozen or more years has been strewn with reports and commentaries on the treatment of mild hypertension. Those who are particularly influenced by the evidence from the insurance companies point to the well-documented increased mortality in the presence of even a little high blood pressure, cite the efficacy of lowering blood pressure by various nonpharmacological and pharmacological means, and urge public education and individual and mass intervention. Others, though not doubting the actuarial data, have not been reluctant to express different views; they have pointed to the limitations of and uncertainties in the findings from the various clinical trials to date and said, "Go slow."

Characteristic of the contrary stands are the comments by Frohlich: "We should still consider that all individuals whose diastolic blood pressure exceeds 90 mm Hg are at increased cardiovascular risk. Moreover, we must still recognize that in these individuals pressure should be reduced in order to minimize that risk." And the comments by Kaplan: "We must not lose sight of the admonition that therapy of asymptomatic hypertension is preventive therapy, not curative. Further, only a minority of hypertensive patients will be saved from disease and death by such therapy. We should do nothing that will add any degree of risk, be it ever so small, to the large majority of mild hypertensive patients who would not suffer if left untreated." It was hoped that the results of the recent Medical Research Council (MRC) Trial might at least partially resolve the controversy.

In brief, the MRC Trial was a clinical trial of drug treatment of mild hypertension (baseline systolic pressure less than 100 mm Hg; diastolic pressure, 90–109 mm Hg). The trial included 17,354 subjects aged 35 to 64 years who were observed for an average of 5½ years. Nearly all were white, and the division between the sexes was almost equal. Most of these participants were members of general practice clinics mainly located in small towns. Excluded were patients already receiving antihypertensive treatment, those known to have diabetes, gout, asthma, angina pectoris, or intermittent claudication, and those who had experienced a recent myocardial infarction or stroke. The trial, which was single blind, provided for random allocation of the participants to four schedules: treatment with a fixed dose (10 mg daily) of a thiazide diuretic (bendrofluazide) or a similar looking placebo, and treatment with graded daily doses up to 240 mg of a β-blocking drug (propranolol) or a similar appearing placebo. No specific advice was given regarding salt intake, obesity, exercise, or smoking.

Treatment with active drugs resulted in substantial drops in blood pressure that were

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well maintained; the declines were slightly greater in the thiazide-treated group than in those for whom the β-blocker was prescribed. In terms of hard endpoints, those men and women receiving active drug therapy experienced a significant drop in fatal and nonfatal strokes as compared with those subjects receiving a placebo, but there were no significant differences in incidence of fatal or overall coronary events or of noncardiovascular deaths. Results of several posthoc subgroup analyses were intriguing, but enigmatic and should be viewed warily because of the small numbers and the fact that they did not represent prior hypotheses. For example, the fatal and nonfatal stroke rates were reduced in both smokers and nonsmokers receiving the thiazide preparation, but only in nonsmokers taking the β-blocker. The coronary event rate, both fatal and nonfatal, was clearly reduced only in nonsmokers receiving the β-blocker. The all-cause mortality was actually increased in women on active treatment, but it was reduced in men receiving the same agents. The importance of any of these secondary observations is unclear.

Not surprisingly, in the placebo group, antihypertensive treatment had to be initiated during the course of the study in approximately 20% of the men and 15% of the women. Within the active drug group, few participants were withdrawn because of excessive elevations of blood pressure, although a supplementary hypertensive agent was given to about one fourth of the subjects. Around 20% of the men and somewhat fewer women were withdrawn because of suspected adverse reactions, and another 20% was lost to follow-up.

Certain additional comments are in order. The study was comparable to others in that the placebo group showed a significant initial drop in blood pressure, related undoubtedly both to the phenomenon of regression to the mean and to adaptation to the clinical and trial environment. It is difficult to draw firm conclusions from the data as to the relative advantages and disadvantages of the diuretic as contrasted to propranolol, as the number of events in the subgroups was modest, especially if classified by sex. The trend suggested fewer fatal strokes in diuretic-treated than in β-blocker-treated men and women, but no differences in relation to fatal heart attacks. Total mortality was similar in the active treatment and placebo categories despite the difference in fatal strokes. This result was not surprising as the number of fatal strokes was only 18 and 27, respectively, offset by an actual excess of fatal coronary events among the treatment participants (106 vs 97).

The conservative final estimate of the authors was that, on the basis of this experience, 850 mildly hypertensive subjects would have to receive antihypertensive drugs for a year to prevent one stroke and there would be no likelihood of a reduction of heart attacks or total mortality.

It was not surprising that the report of the trial produced, on the one hand, data that are not entirely to the liking of either side in the controversy regarding the treatment of mild hypertension and, on the other hand, an interpretation that certainly does not comfort the interventionists. A look back to the findings regarding the therapy of mild hypertension in the VA Cooperative Study Group on Antihypertensive Agents in 1970, the United States Public Health Service Hospitals Cooperative Group in 1977, the Hypertension Detection and Follow-up Program (HDFP) in 1979, the Australian Therapeutic Trial in Mild Hypertension in 1980, the Oslo Trial in 1980, the Multiple Risk Factor Intervention Trial (MRFIT) in 1982, and the European Working Party on High Blood Pressure in the Elderly in 1985, reveals that with the possible exception of the HDFP, the benefits in relation to mortality from cardiovascular events were mixed. For example, the VA Cooperative Study Group findings for men in the blood pressure range of 90 to 114 mm Hg showed that drug treatment significantly reduced deaths from cerebrovascular disease but not from coronary disease. The United States Public Health Service data, again limited to men, included few cardiovascular deaths, but these few failed to show either benefit or hazard from drug treatment. The HDFP findings demonstrated a lessened mortality from both cerebrovascular and coronary disease in the active treatment category, but these benefits did not extend to white women, participants under 50 years of age, or to those with mild hypertension and baseline electrocardiographic abnormalities. The Australian study, which included both men and women, failed to indicate benefit for hypertensive women and for those under 50 years of age. Although there was a significantly reduced incidence of strokes and fatal coronary events in the drug-treated group as a whole, the number of nonfatal myocardial infarcts was slightly greater among those participants receiving medica-
The Oslo investigators found a benefit from treatment in terms of stroke incidence but not in terms of coronary events. The MRFT report of experience with approximately 12,000 men suggested an actual increase in the number of deaths from coronary heart disease among those with hypertension and baseline resting electrocardiographic abnormalities who received antihypertensive drug treatment, chiefly with diuretics. The European Working Party on High Blood Pressure in the Elderly have described their findings in 840 patients over the age of 60 years, 70% of whom were women, which revealed a barely significant reduction in deaths from myocardial infarction in the treatment group, but no significant benefit in terms of death from cerebrovascular disease or from other cardiac causes including sudden death. Toth and Horwitz, who reviewed six of the randomized clinical trials, expressed dismay at what they interpreted as major problems in design, execution, and reporting and concluded that the results "do not support a uniform treatment decision for patients with mild hypertension."

The impressions gained by many who have digested the MRC findings are that they are remarkably similar to those of most of the other trials. Pharmacological treatment has not had a uniformly beneficial influence on the major potentially fatal circulatory diseases of the brain and heart, and such favorable effects as have been shown have been selective. Considering only the hard end point of death, and granted that the periods of observation are relatively brief for a chronic disease such as hypertension, drug therapy as practiced in this setting favorably reduced the rate of fatal strokes, has not lowered the number of fatal coronary attacks, and has not reduced the total death rate.

That the cerebrovascular and coronary vascular beds behave differently with pharmacological therapy to lower blood pressure should occasion no surprise. The complications of coronary atherosclerotic disease do not coincide temporally with those of the cerebral circulation; it is well recognized that heart attacks become a population problem decades before strokes. Hypertension is the dominant factor in strokes and is only one of several in coronary heart disease. The effects of cigarette smoking and of unfavorable blood lipid levels are more marked in relation to the coronary than to the cerebral arterial bed. Spasm is now recognized as a frequent and important aspect of the physiology of the coronary arteries; it seems less important in the arteries of the brain. Embolic events appear more numerous and important in the cerebral than in the myocardial circulation. The physiology and pathology of ischemia and infarction of cerebral and myocardial tissue are not identical. These differences are relevant to our expectations and our therapy. Another factor to be considered in judging the MRC results must include the possibility that currently available antihypertensive drugs may have both good and bad effects on the coronary arteries.

On the basis of our current state of both knowledge and ignorance and considering these latest MRC findings, it would seem to make sense for the practicing physician to adopt for the present the posture that drug therapy for mild hypertension using the traditional agents should be selective and is primarily indicated to prevent strokes and not heart attacks. This may mean pharmacological therapy, especially in blacks, in patients with a family history of strokes, and in patients in whom other risk factors are present, but only observation under less threatening situations. Of course, if the blood pressure can be lowered without drugs, all the better, since not all the actions of the current agents may be salutary. However, it is difficult for most patients who are overweight to lose weight and keep it off, and the benefits of moderate salt restriction are not predictable.

Rather than more of this excellent but traditional type of study, the time would seem to be here for pilot clinical trials of other approaches, including alterations of calcium and potassium intake and use of calcium channel blockers and other, newer pharmacological agents that might eventually have mass application in therapeutic approaches to mild hypertension.

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