Medical Research Council’s Treatment Trial for mild hypertension: an interim report

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Summary
The pilot phase of the British multicentre randomized controlled trial of treatment for mild hypertension has shown: (1) that unselected subjects, aged 35–64 years, with mild hypertension are willing to enter and remain in a long-term trial even though asymptomatic; (2) that the differences of mean systolic and mean diastolic pressure achieved between treated and control subjects is sufficient to produce the expected difference in terminating events with the 18,000 patients calculated as needed for the full-scale trial; (3) that side effects with the two selected active primary regimens (bendrofluazide and propranolol) are common but mild (no serious side effects or toxic reactions have been reported); (4) that the work load imposed by the trial, though considerable during screening and the initiation of patients into the trial, can largely be taken by specially trained nursing staff, and when screening is completed the trial does not impose a heavy burden of follow-up examinations; (5) that there are no adverse psychological effects caused by alerting asymptomatic people to their raised pressure and enrolling them into a prolonged programme of clinical attendance; (6) that the total costs of carrying out a full-scale trial—estimated at about £2m ($U.S. 4m)—are commensurate with the potential annual savings in health service expenditure whether the trial shows treatment to be effective or unwarranted.

Key words: blood pressure screening, drug treatment, multi-centre randomized controlled trial, psychiatry.

Introduction
Before authorizing a full-scale trial to assess the value of treating mildly hypertensive adults, the British Medical Research Council asked for a pilot trial under the guidance of a Council Working Party [membership: Professor W. S. Peart (chairman), Professor A. L. Cochrane, Professor C. T. Dollery, Dr K. G. Green, Dr J. F. Harrison, Professor W. W. Holland, Dr A. F. Lever, Dr T. W. Meade, Professor G. A. Rose, Dr B. C. Smith, Dr P. Wilding and Dr W. E. Miall (secretary)] to determine its feasibility and cost. This paper summarizes the results to date.

Calculations based on national mortality statistics and epidemiological data suggested that 18,000 adults aged 35–64 years would need to be recruited to the main trial and followed for 5 years to determine, at the levels of significance specified, the effectiveness of treatment in reducing the incidence of deaths due to hypertension (ICD 400–404) and vascular lesions of the central nervous system (ICD 430–438), and of non-fatal strokes. The trial would be single blind and designed to give a 95% chance of detecting a 40% reduction in such events, significant at the 1% level. Note that no assumption of benefit in coronary heart disease was built into the design.

Pilot trial
People of either sex in the 35–64 years age range are invited to attend for screening. All are asked to complete a brief psychological questionnaire (Goldberg, 1972) while awaiting their first blood pressure reading. Those with diastolic (phase V) measurements [the mean pressure of two consecutive readings recorded with either a Random Zero Sphygmo-
manometer (Wright & Dore, 1970) or a London School of Hygiene instrument (Rose, Holland & Crowley, 1964) over 90 mmHg or with systolic pressures over 200 mmHg are recalled for a second set of two measurements a week later. Those in whom the mean of the four measurements is found within the 90–109 mmHg diastolic range (provided that the systolic pressure is below 200 mmHg) are eligible for an entry examination, which includes a medical history, physical examination including another two blood pressure measurements, a twelve-lead electrocardiogram, blood and urine tests.

If the screening measurements are confirmed by the examining physician, the subject is invited to enter the trial and is randomly allocated to one of four primary regimens. These are bendrofluazide [0.012 mmol (5 mg) twice daily], propranolol [up to 0.406 mmol (120 mg) twice daily], an inert tablet or observation alone. Supplementary drugs, i.e. methyldopa [initially at 1·184 mmol (250 mg) twice daily] and guanethidine [0·034 mmol (10 mg) mornings], are used if bendrofluazide and propranolol respectively fail to control pressure adequately. Control patients, if their diastolic pressures reach 115 mmHg, are transferred to one of the two active primary drug regimens. Follow-up appointments are fortnightly for 3 months, and then 3 monthly for the rest of the first year, and thereafter at 6 monthly intervals.

Twenty-five clinics selected from general practices, industrial medical centres or screening organizations to cover a wide range of medical practice in the U.K., but largely excluding hospital clinics, are currently collaborating and have entered 1166 patients, of whom 64% have been followed for over a year and 21% for over 2 years. The prevalence of patients considered eligible for the trial is about 4% of the age group.

Results

Lapse rates, withdrawals, etc.

About 75% of patients (70% of men, 80% of women) on the lists of those general practices which have completed screening have been examined. By 2 years after entry 13.1% of treated and 10.7% of control subjects have been lost to follow-up (dropouts). A further 10.0% of treated and 4.7% of control subjects have had their primary treatment changed from that randomly allocated owing to side effects or inadequate blood pressure control, but are still followed in the trial.

Blood pressure control

Compliance with tablet taking, as judged by biochemical changes in those on bendrofluazide and changes in pulse rate for those on propranolol, is satisfactory. By 18 months after entry, among men 4% of treated and 21% of control subjects, and among women 6% of treated and 35% of control subjects, have systolic pressures exceeding 160 mmHg. For diastolic pressures exceeding 100 mmHg comparable rates for men are 2% and 14%, and for women 6% and 16%.

The mean differences in pressure between treated and control subjects at 18 months are 13 mmHg systolic, 6 mmHg diastolic for men, and 17 mmHg systolic and 7 mmHg diastolic for women. Recalculations of the numbers of subjects required for the main trial, based on these findings from its pilot phase, conform 18,000 to be of the right order of magnitude.

Control of pressure is similar in those randomly allocated to bendrofluazide to that achieved in those allocated to propranolol but at the expense of a greater need for supplementary therapy. By 18 months after entry, 28% of men on bendrofluazide required a supplementary drug compared with 7% of men on propranolol; at that stage 19% of women on bendrofluazide and 10% on propranolol needed a supplementary drug.

Side effects

By 18 months after entry 17% of men on bendrofluazide and 7% on propranolol had been withdrawn from their randomly allocated treatment on account of side effects; the comparable rates for women were 10% and 13%. The numbers withdrawn are still too small to warrant an analysis of the reasons for withdrawal. No serious toxic reactions have been encountered.

Psychiatric study

Two hundred and ninety participants in the trial have been matched by age and sex with control subjects not in the trial. Both the participants and the control subjects are screened at intervals by the General Health Questionnaire. A positive response
to this indicates psychiatric disturbance, in which case a diagnostic psychiatric interview is carried out on those so indicated.

The results so far show, in comparison of trial participants with control subjects, that there is no difference in the incidence of psychiatric disorder between screening and entry into the trial. However, after entry the amount of psychiatric disturbance becomes significantly less in those in the trial. This finding results from the greater improvement of those entering the trial with a diagnosed neurotic illness, compared with control subjects over the same period. The significance of this finding is being examined further.

Discussion

The MRC Working Party, on the basis of the data summarized above, believes that it has already shown that a definitive trial is scientifically feasible and ethically justified. It has not yet demonstrated that the pilot trial could be rapidly expanded in the U.K. to the size necessary for the full-scale venture.

For the full trial 90,000 person-years of observation have to be purchased and, by extrapolation from the pilot trial, the estimated total cost would be about £2.5m ($U.S.5m). With self-contained and independently staffed mobile screening clinics the screening could probably be undertaken more rapidly, resulting in savings and an overall cost of about £2m.

In considering the value of a full-scale trial it is important to consider two possible outcomes: (a) that treatment will be shown to be effective and (b) that it will be shown to be unwarranted. It is unlikely that a result favouring treatment will lead to a recommendation that all subjects with mild hypertension be treated. Such trials, of which there are several in progress (World Health Organization, 1975), are likely to reveal (from their large control groups) the characteristics of those mild hypertensive subjects at greater risk of complications; from their treated groups they should reveal the characteristics of those likely to derive more or less benefit from treatment.

If treatment is shown to be effective, the costs of treatment have to be balanced against the benefits of savings in in-patient treatment, time lost from work, etc. If treatment is shown to be unwarranted, the costs of the trial have to be balanced against the savings which will result from that finding. Already there is a trend, encouraged by the pharmaceutical industry, to treat hypertension earlier despite doubt concerning the evidence on the effectiveness of such treatment. This trend is greater in the U.S.A. than in Britain, but a negative result from the trial would do much to prevent a costly drift into unnecessary and unwarranted treatment.

The direct costs to the National Health Service in Britain for cerebrovascular disease were estimated (at 1969 prices) to be £41.9m per annum, and for ischaemic heart disease to be £27.5m per annum (Office of Health Economics, 1971). If the incidence of either or both of these major complications of hypertension could be reduced by controlling it more effectively, there could be a major saving of money currently devoted to curative services to set against the increased cost of prevention. It could be argued that the cost of obtaining information from trials such as this is at least commensurate with the potential savings, whether they show treatment to be of value or unwarranted.

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References