Randomised controlled trial of treatment for mild hypertension: design and pilot trial

Report of Medical Research Council Working Party on Mild to Moderate Hypertension*

British Medical Journal, 1977, **1**, 1437-1440

Summary

A multicentre pilot trial to assess the feasibility of undertaking a full-scale national trial of treatment for mild to moderate hypertension has been performed and is being continued. By February 1977 over 1800 patients had entered the trial and some have been under observation for over three years. The results so far show that the definitive trial is administratively and scientifically feasible and ethically justified.

Introduction

The effectiveness of drug treatment in hypertension has been established by controlled trials in severely hypertensive men,[1] patients with uncomplicated hypertension with diastolic (phase IV) pressures exceeding 110 mm Hg,[2] pregnant women,[3] and survivors of strokes.[4 5] Men with sustained diastolic (phase V) pressures of 90-114 mm Hg also seem to benefit from drug treatment[6] but more evidence is needed[7] and no large scale trial has reported results for women with blood pressures in this range. None of the trials have shown that treatment has a significant effect in preventing ischaemic heart disease.

Insurance statistics and epidemiological data show steadily increasing risks with each increment of systolic or diastolic pressure even within the range of levels that are generally accepted as normal; there is no suggestion of a threshold at which mortality suddenly increases (fig 1).[8] The benefits of treatment are likely to relate to the risks but have to be weighed against the costs; these include the nuisance to asymptomatic people of prolonged treatment with drugs that may have side effects.

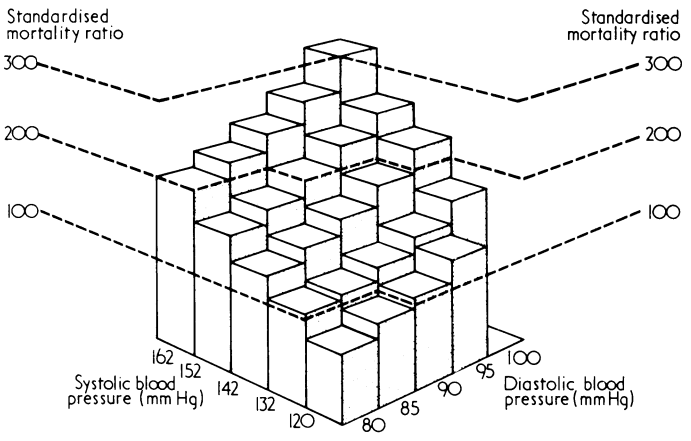

FIG 1—Mortality according to systolic and diastolic blood pressures in men aged 40-69 years. Diagram is adapted from Society of Actuaries build and blood pressure study 1959.

Design of trial

In 1971 an ad hoc committee advised the Medical Research Council on the need for a British study and recommended that it should determine the effectiveness of antihypertensive treatment in adults aged 35-64 years, of either sex, with diastolic (phase V) pressures of 90-109 mm Hg. A trial was designed to give a 95% chance of detecting a 40% reduction in the number of deaths due to hypertension (ICD 400-404) and stroke (ICD 430-438) and in the number of non-fatal strokes, significant at the 1% level after five years' follow-up of the people taking part.

Calculations, based on epidemiological data and the Registrar General's mortality statistics, indicated that 9000 men and 9000 women would be required in each of the treatment and control groups if significant results were to be obtained for the separate sexes—that is, 36 000 people. If, however, antihypertensive treatment were to confer equal benefit for the two sexes—and in terms of the complications specified in the trial design there is no reason to expect otherwise—18 000 subjects (9000 treated and 9000 controls) would suffice. About 5% of the population appear to be eligible for the trial and, allowing for those unwilling or unable to enter and remain in it for the required time, about half a million adults would have to be screened. The trial would be a single-blind study based on general practices,

*WORKING PARTY

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).

PARTICIPANTS

Monitoring committee—Professor G A Rose (chairman), Dr M W Adler, Mr P Brennan, Dr E C Coles, Dr M Hamilton, Dr J A Heady, Dr T W Meade, Dr W E Miall, Dr E B Raftery.

Ethical Committee—Professor Sir Richard Doll (chairman), Dr J Fry, Dr J A Heady, Dr M Hamilton, Dr P Taylor.

Co-ordinating Centre, MRC-DHSS Epidemiology and Medical Care Unit, Northwick Park Hospital, Watford Road, Harrow, Middlesex HA1 3UJ

P Brennan, M R Copson, J Fisher, P Jenkins, W E Miall, S Standring, A Sydow, J Tudhope, J Wilderspin.

Physicians

A Bailey, B K B Bain, A Balmforth, D G Beevers, L A Birchall, J D Broadbent, C J Burns-Cox, C Carty, J D Cameron, M H F Coigley, H Conway, D Cresswell, R F Davies, R Davis, N A Duncan, G W Edward, D M Fleming, E H Fulton, W Gibson, M P Gilbert, A A Graham, E R Greene, D J Handford, V Hawthorne, P M Higgins, J Hodson, C D Holland, A L M F Hollingworth, S Hussain, B Jarman, D M Jones, W Kerns, E L Knowles, L P Mackie, S McCormack, K MacPherson, I McRobbie, F S Matthews, J Matthias, K W Miller, C M Molloy, D E Morton, H Nicol, P L Padfield, K G Poyner, T P C Schofield, A J M Slovak, B C Smith, R N Smith, G M Stewart, R G Taylor, A K Trimm, F Tunbridge, R M Turner, G D Walker, H A Wapshaw, J Waters, J Watt, H H Whincup.

Nurses and others

C A Atherton, G Barnes, P Barr, J Begg, D J Bird, K Brown, A Butler, M Callow, M A Chivers, E Coleman, L Cotterill, I Craig, B Cundy, S Duncan, S A Edwards, C Evans, Y Ewart, J Gartside, N Ginnelly, J Godball, M Grant, S Hanley, R Harrup, B S Hebbron, A Henderson, S Hiller, M Iball, D Jolley, H Jones, B Kelly, F-A King, G Lawson, S Lewis, R Lloyd, R Lockie, K Lowe, M O Lumley, K Marcus, A Mees, I Milligan, A J Muldoon, M Pearson, A Pollard, Y Shepard, R Warner, A Williams, H Wright, R D Wood, J M Young.

Wolfson Research Laboratories, Queen Elizabeth Medical Centre, Birmingham

Professor T Whitehead, Dr P Wilding.

Institute of Psychiatry

Dr A H Mann, Professor M Shepherd.

industrial clinics, and screening organisations rather than on hospital hypertension clinics.

An MRC working party was appointed to carry out a pilot trial and advise on the feasibility of the full-scale investigation. The pilot trial is continuing but we summarise here our findings so far (up to February 1977).

Pilot trial

METHODS

Screening

Men and women aged 35-64, mostly from defined populations (general practice registers, industrial work forces, etc), were invited to attend for blood pressure screening at clinics or a mobile van, where specially trained nurses recorded two casual measurements (sitting after 10 minutes' rest) using either the Hawksley Random-Zero[9] or the London School of Hygiene[10] sphygmomanometer. Those with mean pressures of over 200 mm Hg systolic or 90 mm Hg diastolic (phase V) attended again a week later when two further measurements were taken. If, after the second visit, the mean of the four measurements equalled 200 mm Hg or more systolic or 110 mm Hg or more diastolic the patient was considered ineligible for the trial and referred for further investigation and treatment. If the arterial pressure was below 200 mm Hg *and* below 90 mm Hg he or she was reassured. Others with diastolic pressures of 90-109 mm Hg (and systolic pressures below 200 mm Hg) were invited to attend for a physicial examination at which two further blood pressure measurements were taken, this time by a doctor.

If the screening measurements were confirmed the nature and purpose of the trial was explained, consent forms were signed by those willing to participate (and by their family doctors), and an entry examination including electrocardiogram (ECG) and blood and urine tests was carried out. Unless reasons for exclusion were found the patients were randomly allocated to one of four treatment regimens. Grounds for exclusion from the trial were: (*a*) a known underlying cause of hypertension (secondary hypertension); (*b*) antihypertensive treatment in the previous three months; (*c*) normally accepted indications for treatment (ophthalmic, renal, or cardiac); (*d*) previous myocardial infarction or stroke within last three months; (*e*) angina pectoris or intermittent claudication; (*f*) concurrent serious disease; (*g*) pregnancy, diabetes, gout, or bronchial asthma; (*h*) history of significant psychiatric disorder; (*i*) serum potassium concentration of 3·4 mmol(mEq)/l or below; or (*j*) blood urea of 8·3 mmol/l (50 mg/100 ml) or above.

Therapeutic regimens

The pilot trial was designed to use two distinct primary regimens—a thiazide diuretic (bendrofluazide, 5 mg twice a day) and a beta-blocker (propranolol, in increasing doses up to 240 mg/day) with supplementary drugs for those responding inadequately. Propranolol or methyldopa were used to supplement the thiazide; bendrofluazide or guanethidine were the supplements for propranolol. Matching placebos for the primary drugs were given to controls, but if their diastolic pressures reached 115 mm Hg they were transferred to the corresponding active drug.

Follow-up

Follow-up visits, at which symptoms were noted, pressures recorded, tablets counted, and further supplies provided, were arranged fortnightly for three months, then quarterly to one year, and thereafter every six months. Much of the work was undertaken by a nurse with ready access to medical advice. At the end of each year a fuller examination was carried out by the doctor. The additional work imposed by the trial for a general practice with a list of 10 000 patients is shown in fig 2. At the height of screening 200 additional appointments a month were made for patients to see the nurse.

The trial load diminishes once screening is completed. The practice with 10 000 patients now requires two nurse sessions and one short session for the doctor each week to cope with the follow-up load. The mobile caravan unit can screen 85-90% of the 35-64 age range for a practice with a total list of 10 000 in about five weeks with less interruption of other clinical activities.

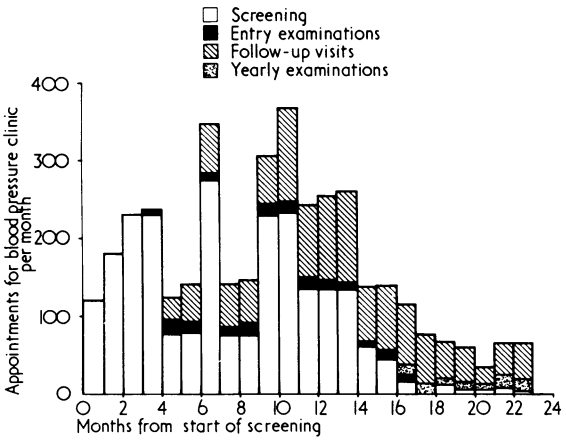

FIG 2—Additional work load created by MRC trial in a general practice with 10 000 patients.

Analysis

The six main objectives of the trial were: (*a*) to recruit 500-1000 patients aged 35-64 with diastolic (phase V) pressures of 90-109 mm Hg; (*b*) to show whether the procedures were acceptable to asymptomatic people; (*c*) to show whether the drugs controlled pressure without unacceptably high rates of side effects; (*d*) to examine the cost and efficiency of different types of clinics; (*e*) to determine the psychological implications of alerting asymptomatic people to their raised blood pressure and enrolling them into a prolonged programme of clinic attendance; (*f*) to assess the feasibility of expanding to a full-scale trial. The results of this pilot trial were analysed in relation to these six objectives.

RESULTS

Recruitment into trial

Twenty-five centres, selected to represent a wide spectrum of medical practice but avoiding hospital clinics, are currently collaborating; nine are industrial clinics, five are linked with screening organisations, and 11 are general practice groups. By February 1977 these clinics had entered 1849 people into the trial (1092 men, 757 women), of whom 972 have been under observation for more than one year, 629 for over two years, and 219 for over three years.

Acceptability

Acceptability was assessed at screening and entry and after entry in terms of compliance with tablet taking, dropout rates, and the reactions of clinics and patients. In the general practices 75-90% of the age range were screened, although problems with inaccurate age and sex registers made it difficult to be certain of the figure. Nevertheless, over 90% of eligible patients entered the trial. After one year 87% of patients had taken at least 75% of the tablets prescribed to them as judged by tablet counts, and the biochemical changes in those on bendrofluazide (fig 3) and the pulse rate changes in those on propranolol (fig 4) suggested that compliance was usually satisfactory.

By three years after entry, 82% of men and women who had entered the trial were still under observation. The remaining 18% included those who stopped of their own (or their general practitioner's) volition, those who left the district, and those who died.

Clinics have welcomed the trial as an opportunity to deal systematically with the problem of hypertension in the populations they serve, and patients seem to have appreciated their doctors participating in an investigation of preventive measures.

Control of blood pressure and side effects

Differences in mean pressure between treated and control subjects (13-17 mm Hg systolic, 6-8 mm Hg diastolic two years after entry), though highly significant ($P < 0.001$ for each sex and systolic and

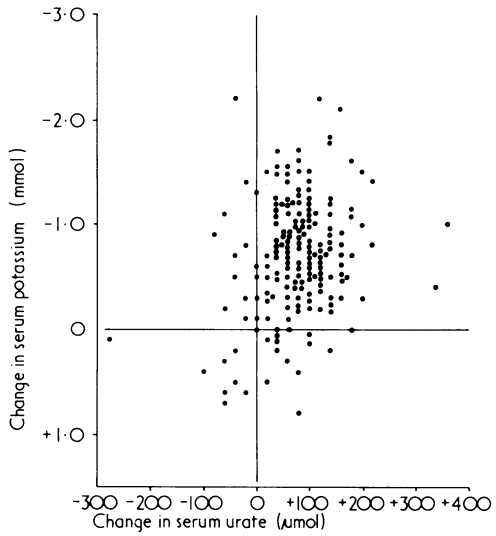

FIG 3—Change in serum potassium and serum urate concentrations from entry to one year in those taking bendrofluazide.
Conversion: SI to traditional units—Urate: 1 μmol 0·168 mg. Potassium: 1 mmol 1 mEq.

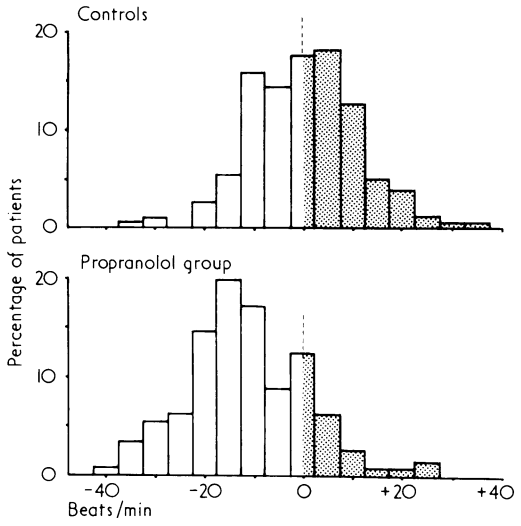

FIG 4—Change in pulse rates from entry to first annual examination in controls and propranolol group (both sexes).

diastolic pressures), were less than expected because the fall in pressure in the controls was greater and more prolonged than expected (fig 5). This fall in pressure in people taking inert tablets was further investigated by including a subgroup of controls who attended clinics at the same frequency but were only under observation. They showed changes in pressure identical with those found in patients receiving placebo. The fall in pressure in the control group was therefore attributed to habituation to clinic procedures and regression towards the norm and was independent of the tablet itself.

The distributions of pressure among treated and control groups at the first annual examination were used to re-estimate the numbers required for the full-scale trial and confirmed that the estimate of 18 000 is about right.

Control of pressure was similar with the two drug regimens but more of those on a diuretic required a supplementary drug. No serious drug reactions were reported. After two and a half years 21% of men and 9% of women on bendrofluazide and 8% of men and 15% of women on propranolol have had to stop taking their allocated treatment because of minor and reversible side effects. Most were transferred from one active primary regimen to the other and continued treatment.

Biochemical investigations were carried out centrally for all participants at entry, three months after entry (for those on diuretic), and at the end of each year. The changes in serum biochemical values from entry to the first annual examination and from the first annual examination to the second are shown in table I. The rise in serum urea and urate and the fall in serum potassium concentrations for those on thiazide diuretic were expected; all were highly significant when compared with the changes in control subjects. The thiazide groups showed no significantly greater change in casual blood glucose than controls, though an increase in the first year, followed by a fall in the second, occurred in both sexes. The increases in serum cholesterol in those on thiazides were statistically significant for the interval from entry to one year ($P < 0.01$ for men, $P < 0.05$ for women). Those taking propranolol showed significant increases in serum urate and serum potassium concentrations in the first year in both sexes, and the women also showed a significant rise in blood urea concentration.

Cost and efficiency of different types of clinic

In the present economic climate industrial clinics have proved difficult to recruit. They are efficient and less costly (to the MRC) but require longer negotiations with management and unions before

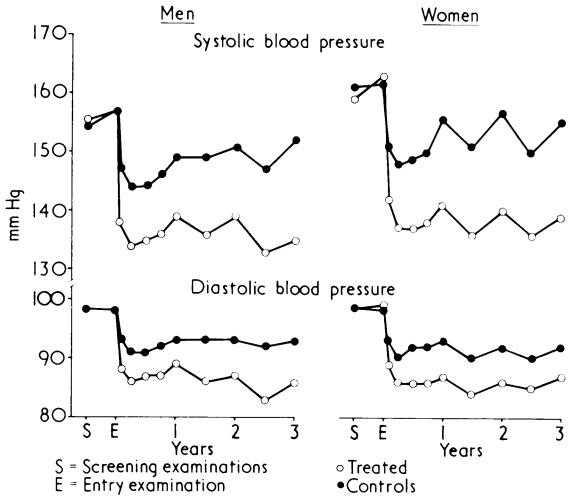

FIG 5—Mean blood pressures within three years of entry to trial in controls and treated patients.

TABLE I—*Changes in serum biochemical values in the first two years of the trial according to primary therapeutic regimen and sex*

	Men		Women	
	Entry to 1 year	1–2 years	Entry to 1 year	1–2 years
Serum urea (mmol/l)				
Bendrofluazide group	+0·68***	+0·43	+0·68***	+0·40
Propranolol group	0	+0·23	+0·63***	+0·10
Control group	+0·12	+0·23	+0·08	+0·33
Serum urate (μmol/l)				
Bendrofluazide group	+83***	−18	+66***	−18
Propranolol group	+24***	−6	+18***	0
Control group	+6	0	−6	−6
Serum potassium (mmol/l)				
Bendrofluazide group	−0·6***	+0·1	−0·7***	0
Propranolol group	+0·2***	0	+0·2***	0
Control group	0	0	0	0
Serum sodium (mmol/l)				
Bendrofluazide group	0	−0·2	−0·3	+0·6
Propranolol group	+0·4	+1·0	+0·5	+0·1
Control group	+0·6	+0·5	+0·3	+0·5
Blood glucose (mmol/l)				
Bendrofluazide group	+0·17	−0·38	+0·29	−0·45
Propranolol group	−0·04	−0·23	−0·21	−0·06
Control group	+0·07	+0·09	−0·01	−0·29
Serum cholesterol (mmol/l)				
Bendrofluazide group	+0·21**	+0·10	+0·17*	+0·13
Propranolol group	+0·07	−0·07	−0·07	+0·21
Control group	0·003	+0·05	−0·02	+0·24

Significantly different from change in controls: *** at 0·1% level, ** at 1% level, * at 5% level.
The sizes of groups varied slightly according to test. For entry to 1 year there were about 105 men on bendrofluazide, 105 on propranolol, and 230 controls and about 85 women on bendrofluazide, 70 on propranolol, and 155 controls. For 1 to 2 years the corresponding numbers were 55, 55, and 120 men and 55, 55, 100 women.
Conversion: SI to traditional units—Urea: 1 mmol/l ≈ 6 mg/100 ml. Urate: 1 μmol/l ≈ 0·017 mg/100 ml. Potassium and sodium: 1 mmol/l = 1 mEq/l. Glucose: 1 mmol/l ≈ 18 mg/100 ml. Cholesterol: 1 mmol/l ≈ 38·6 mg/100 ml.

starting and have contributed only 18% of the person-years of observation included in the pilot trial. Most of the large-scale screening projects known to the working party and suitable for inclusion in the trial have been included. They are usually efficient and marginally less costly to the Council than general practice clinics. General practices require additional MRC-supported staff, are a little more expensive, but offer the best prospects for future expansion. Group practices in small towns seem to be the most successful and are likely to be more useful to the trial than those in conurbations, new housing estates, or isolated rural areas. Mobile screening facilities are being assessed for general practices that have inadequate space to devote to a rapid screening programme.

A comparison of the costs per person year of observation and of dropout rates between different types of clinic is shown in table II. It should be emphasised that these were costs to the Medical Research Council not national costs. Much of the work was done voluntarily by doctors and nurses paid from other funds.

TABLE II—*Costs and dropout rates in different types of clinic*

Type of clinic	Costs per person year (£)	No of dropouts per 100 person years
Industrial clinics	15·11	10·0
Screening organisations	21·62	6·3
General practices	25·31	7·2
Average	22·47	7·4

Psychological implications

A self-administered questionnaire, the 30-question version of the Institute of Psychiatry's general health questionnaire,[11] was completed by most subjects in some clinics before blood pressure screening and were given again at intervals to all those who subsequently entered the trial and to matched controls who were reassured by either the first or the second screening examinations. Positive responders underwent a standard psychiatric interview. By these means we could measure the incidence of psychological disturbance and determine at which stage it developed and whether it was influenced by therapeutic regimen. It could also be related to the personality of the subject affected.

Preliminary results were entirely reassuring. The incidence of psychological disturbance was no higher in trial patients than in controls between first screening and trial entry nor was the subsequent incidence in trial participants greater than that in controls. People with neurotic symptoms who entered the trial had a significantly greater "cure rate" for their neurotic symptoms than those who did not enter the trial. This finding will be reported elsewhere[12] and is being further investigated.

Feasibility of expanding to full-scale trial

Twenty-five clinics participated in this pilot trial. A further 70 clinics, some of which will be enrolled this year, are willing to start. Though this is fewer than the 200 clinics required for the full-scale trial, previous experience suggests that each of the 95 clinics mentioned above would be in a position to recruit one or more additional centres

Discussion

The evidence summarised here suggests that a full-scale trial would be scientifically and ethically justified and administratively feasible. The main objectives of such a trial would be to show whether drug treatment of mild hypertension prevents serious cardiovascular complications and to establish criteria for determining whether it does more good than harm. It is unlikely that such a trial would lead to general recommendations that all adults with pressures above some point on a blood pressure distribution should be treated. The large control groups should make it possible to specify the characteristics of people with mild hypertension who are at greater risk of complications, and the differences between the treatment and control groups should make it possible to determine the characteristics of those likely to derive more or less benefit from treatment.

Large collaborative trials of this kind are expensive but have the potential for improving the health and medical care of many people. Extrapolation from the experience in the pilot phase of this trial indicates that the 90 000 person-years of observation required for the main study would cost about £2 million, spread over eight to 10 years.

The cost of diseases related to hypertension is probably increasing in all Western societies. In the USA expenditure on antihypertensive drugs rose from $118m in 1965 to $383m in 1975 partly as a result of the acceptance of the results of the Veterans Administration trials.[13] The results of the Veterans Administration study for participants with diastolic pressures of 90-114 mm Hg[6] have not, however, been internationally accepted as being of direct relevance to those who deliver primary medical care, who will presumably remain responsible for starting treatment for most hypertensive patients. This estimated cost of £2m for the full trial in Britain should be put in the context of the annual expenditure on antihypertensive drugs and diuretics used for hypertension, which in 1975 was estimated at £28m, and of the £2-3m spent annually by the British pharmaceutical industry in advertising antihypertensive agents.[14]

The potential for reducing morbidity and mortality from the complications of mild hypertension justifies the careful assessment of the value of treatment which can best be provided by a large collaborative trial. "Mild hypertension—to treat or not to treat?" This is an important question and requires an authoritative answer.

The Working Party gratefully acknowledges the excellent collaboration of the physicians and nurses in the pilot trial. Thanks are also due to the staff at the co-ordinating centre (address below); Mr Patrick Brennan for computing and statistical control; Dr A H Mann for the psychiatric investigations; the staff of the Wolfson Research Laboratories, Queen Elizabeth Medical Centre, Birmingham, for all biochemical testing; Glaxo (for tablets of bendrofluazide and its placebo); Imperial Chemical Industries (for generous financial support and for tablets of propranolol and its placebo); Ciba (for supplies of guanethidine); and Merck, Sharp and Dohme (for providing a mobile screening unit and funds for its staffing, and for supplies of methyldopa).

Requests for reprints should be addressed to Dr W E Miall MRC-DHSS Epidemiology and Medical Care Unit, Northwick Park Hospital, Watford Rd, Harrow, HA1 3UJ.

References

1 Veterans Administration Co-operative Study Group, *Journal of the American Medical Association*, 1967, **202,** 1028.
2 Hamilton, M, Thompson, E N, and Wisniewski, T K M, *Lancet*, 1964, **1,** 235.
3 Leather, H M, *et al*, *Lancet*, 1968, **2,** 488.
4 Carter, A B, *Lancet*, 1970, **1,** 485.
5 Hypertension-Stroke Co-operative Study Group, *Journal of the American Medical Association*, 1974, **229,** 409.
6 Veterans Administration Co-operative Study Group, *Journal of the American Medical Association*, 1970, **213,** 1143.
7 World Health Organisation. Report of a Joint WHO-ISH Meeting, Madrid 1975. (Obtainable on request from WHO, Geneva.)
8 Society of Actuaries, *Build and Blood Pressure Study*, vol 1. Chicago, Society of Actuaries, 1959.
9 Wright, B M, and Dore, C F, *Lancet*, 1970, **1,** 337.
10 Rose, G A, Holland, W W, and Crowley, E A, *Lancet*, 1964, **1,** 296.
11 Goldberg, D P, *Detection of Psychiatric Illness by Questionnaire*. London, Oxford University Press, 1972.
12 Mann, A H, *Psychological Medicine*. In press.
13 *British Medical Journal*, 1976, **2,** 1025.
14 Fryer, J H, 1976, personal communication.

(*Accepted 4 April 1977*)