The large studies in hypertension: What have they shown?

J. I. S. ROBERTSON

Medical Research Council, Blood Pressure Unit, Western Infirmary, Glasgow G11 6NT

Introduction

In an adult western (or westernized) population, both systolic and diastolic blood pressure levels are distributed continuously; there is no point of demarcation separating hypertension from normal blood pressure (Pickering, 1961; Swales, 1985). Nevertheless, an abundance of epidemiological evidence has demonstrated that those people whose blood pressures lie towards the upper end of the distribution are at increased risk of a variety of adverse cardiovascular events (Robertson, 1983a, 1984, 1987), specifically, stroke, cardiac failure, coronary heart disease, progressive renal impairment and, more rarely, the malignant phase. The risk of these events is graded quantitatively in proportion to the arterial pressure. While the relative risk of higher pressures is seen in both sexes, the absolute risk is less in women. Consequently, it has been more difficult to show benefit from therapeutic intervention in women. Cardiovascular hazards and the pattern of adverse events are also modified by a variety of other influences, including race, social circumstances and, most importantly, smoking.

The benefits of antihypertensive drug therapy have long been established in the malignant phase and in hypertensive heart failure (Robertson, 1983a, 1984). However, the value of prophylactic treatment has been more difficult to establish (Robertson, 1987). Over the 21 years before 1985, a series of trials was conducted with varying competence, which progressively lowered the threshold of arterial pressure above which a protective effect against complications could be seen from antihypertensive drug therapy (Hamilton *et al.*, 1964; Veterans Administration Cooperative Study Group on Antihypertensive Agents 1967, 1970, 1972; Australian Therapeutic Trial in Mild Hypertension 1979, 1980, 1981). With varying degrees of conviction these studies demonstrated the benefits of antihypertensive drug therapy in preventing stroke, cardiac failure and renal deterioration. Interestingly, none of the controlled trials before 1985 had provided convincing evidence of protection against coronary heart disease, although hyper-

tension is undoubtedly a risk factor for that condition (Robertson 1983a, 1984, 1987). I, and others (Beevers, 1983; Hampton, 1983, 1984; Ramsay, 1984; Toth & Horwitz, 1983; Freis, 1982), have previously reviewed the earlier trials in some detail elsewhere.

An early retrospective analysis (Newman & Robertson, 1959) showed that cardiovascular complications were less frequent the more effectively blood pressure was controlled. As will be seen, this observation is relevant to much recent work.

The prospective study of Hamilton and colleagues (1964) demonstrated a protective effect of antihypertensive therapy in adults whose IVth phase diastolic pressures were at or above 110 mm Hg and who were, at the outset, free from overt cardiovascular damage. Stroke, in particular, was less frequent in those who received antihypertensive drugs than in those who did not. In retrospect, the trial has some defects. The numbers of patients entered were small. While a significant effect was seen in the study both overall and in men, there was only suggestive benefit in women. Nevertheless, women who complied with treatment and whose blood pressure was well controlled did better than those whose hypertension was inadequately reduced.

The Veterans Administration trial (Veterans Administration Cooperative Study Group on Antihypertensive Agents 1967, 1970, 1972) was for many years the most frequently quoted trial, and a large part of the case for preventive antihypertensive therapy was based upon it. Nevertheless, in the light of current clinical trial techniques, it has obvious blemishes. A major drawback is that the Veterans Administration trial dealt only with men; therefore, no evidence can be derived from it concerning antihypertensive treatment in women. The patients were severely diseased; no less than 60% had evidence of cardiovascular abnormalities at entry. The statistical methods employed would now be regarded as distinctly unorthodox. Subsets of patients were analysed retrospectively; those

who dropped out of the trial were not followed up; most importantly, the results were apparently inspected continually by the review committee and the trial seems to have been terminated arbitrarily rather than according to predetermined criteria. Thus, although the reports based on this trial have been widely used to justify protective antihypertensive therapy in patients with Vth phase diastolic pressures that remain at or above 105 mm Hg, it is a rather insecure base on which to rest firm recommendations. Hampton (1983, 1984) has pointed out that the study broke many rules of trial techniques now considered mandatory and has described it as 'a very odd trial indeed'. In his view, the Veterans Administration study 'probably would not be accepted for publication in any reputable journal today'. This speculation is, of course, not susceptible to testing. While there may be some injustice in subjecting a pathfinding trial to criticism of a later era, it is perhaps as well to be reminded of the shortcomings of the Veterans study.

The Australian Treatment Trial of Mild Hypertension (1979, 1980, 1981) was more recent and benefited from the earlier mistakes. In Hampton's view (1984) this was, in 1984, the 'only study so far published that has any pretence to respectability'. The Australian trial provided evidence that adults, male or female, whose Vth phase diastolic pressure remained at or above 95 mm Hg, benefited from prophylactic antihypertensive therapy. In the 2000 days of the trial, there was a highly significant reduction in all trial end-points in those who received active treatment. Furthermore, deaths from all causes during the course of the trial were significantly less in those who received antihypertensive drugs. Importantly, there were nearly 600 patients over 60 years old at entry; again, there was a significant reduction in trial end-points with active treatment in these elderly subjects. A critical aspect, which had been hinted at in earlier reports, was that the average diastolic pressure in the course of the study was a powerful predictor of complication rate. The Australian study, nevertheless, does not by any means escape criticism. Although large, with nearly 4000 trial entrants, it was not large enough. The results were significant only for those patients who remained in the trial and adhered to the protocol. When drop-outs and withdrawals were also taken into account ('intention-to-treat' analysis), the results were statistically inconclusive. Furthermore, the elderly subset was not defined at the outset. Therefore, although the benefits in those over 60 years old were encouraging, this part of the analysis was retrospective and must be scrutinized with appropriate caution. It should also

be emphasized that the gains from active therapy, although statistically significant, were numerically modest.

The United States Hypertension Detection and Follow-up Program (HDFP) (1979a, b, 1982) remains the largest, most expensive and by far the most controversial of all the treatment trials of hypertension reported. The main controversy centres on the fact that it was not a strictly controlled study. Patients entering the HDFP were randomly allocated to one of two groups. One group of patients received 'stepped care' when they attended a special hospital clinic, were given antihypertensive drug therapy according to a predetermined protocol, and also usually received advice concerning the restriction of intake of alcohol and salt, on dietary modifications designed to reduce serum cholesterol, and anti-smoking counselling. The control group ('referred care') comprised patients simply referred back to their usual medical practitioner to receive whatever therapy he or she might deem appropriate. It is therefore clear that the trial results were determined by a variety of factors other than control of high blood pressure. The design evidently biased the outcome in favour of greater benefit in the stepped-care group. One interesting feature of the HDFP, which distinguishes it from those described above, is that patients in the stepped-care group whose entry diastolic pressures were in the range 90–104 mm Hg had fewer myocardial infarctions during the course of the trial than the referred-care patients. There must be a strong suspicion that this may well have been due to influences other than antihypertensive therapy (Hampton, 1983, 1984; Ramsay, 1985; Toth & Horwitz, 1983).

The proponents of the HDFP (Hypertension Detection and Follow-up Program Cooperative group, 1982; Moser 1983; Moser & Gifford, 1985) interpret the results as justifying prophylactic antihypertensive treatment in adults whose diastolic pressures remain at or above 90 mm Hg. Critics of the trial deny this. Hampton (1983, 1984) in particular has been especially severe on this study. In Hampton's view the HDFP 'ought to be rejected because it was not a proper trial of the treatment of hypertension . . . it was large and involved a lot of work and expense but its value is very limited'. Unsurprisingly, Moser, one of the advocates of HDFP, has replied (1985): 'I find Hampton's arguments less than persuasive', a riposte remarkable for its moderation in view of the severity of the attack. Another critic, Beevers (1982), has commented: 'HDFP is a strange study . . . plenty of data but not much information'. In rebuttal, Maxwell of

Los Angeles has stated firmly (1982): 'HDFP is not a 'strange study'. HDFP continues to be defended with spirit (Moser & Gifford, 1985; Moser, 1985). Even so, as Ramsay (1985) has pointed out, not unfairly, 'We shall never know how much of the overall benefit observed was due to antihypertensive treatment and how much to . . . other factors, and no amount of statistical analysis or advocacy can remove this doubt'.

The earlier Gothenburg trial (Berglund *et al.*, 1978) has many similarities to HDFP, although interpretation has been much more cautious. In the Gothenburg study, men with hypertension were treated either in a special hospital hypertension clinic or by their usual medical practitioner. Although those attending the hospital had initially slightly more severe hypertension, they fared better over the period of trial, in particular having significantly fewer fatal and non-fatal heart attacks. Interestingly, they also suffered fewer deaths from non-cardiovascular causes. The Swedish workers suggest that more effective control of hypertension in the hospital clinic is likely to have been a major factor in limiting cardiovascular complications. Moreover, the significant lowering of both fatal and non-fatal heart attacks could have been due to greater reliance on β -adrenoceptor blockers for hypertension treatment in the hospital clinic. However, it is also emphasized by the authors that closer medical supervision and care in the hospital clinic probably played a part in producing the more favourable outcome. This suggestion is supported by the reduction in deaths from causes other than cardiovascular disease. Thus, there are, as in HDFP, substantial problems in attempting to discern the beneficial effects of antihypertensive therapy.

The studies mentioned show that certain of the vascular complications of hypertension, notably the malignant phase, cardiac failure, progressive renal impairment and stroke, can be corrected or prevented by antihypertensive drug therapy. With the possible exceptions of HDFP and the Gothenburg trial, which were subject to important reservations, until 1984 no comparable protection had been seen against coronary heart disease.

Two further studies deserve mention: both have been cited (Ramsay, 1985) in emphasizing the modest numerical benefits to be derived from antihypertensive treatment. The US Public Health Service Study (McFate-Smith, 1977) entered male and female subjects whose Vth phase diastolic pressures were in the range 90–114 mm Hg after 3 months of observation on placebo. One hundred and ninety-three were randomized to active therapy (chlorothiazide

plus rauwolfia) and 196 to placebo. Active therapy lowered average blood pressure from an initial 148/99 mm Hg by 16/10 mm Hg. After a mean 7 years follow-up, deaths (two *vs* two) and morbid events (eight *vs* nine) were similarly frequent in the treated and placebo groups. The Oslo Study (Helgeland, 1980; Leren & Helgeland, 1986) dealt with men aged 40–49 years with blood pressures in the range 150–179 mm Hg systolic and/or 95–109 mm Hg Vth phase diastolic. Patients were variously allocated to antihypertensive therapy (hydrochlorothiazide and methyl-dopa or propranolol, $n = 406$) or no treatment ($n = 379$). After 5.5 years, during which blood pressure was lowered on average by 17/10 mm Hg by treatment, the number of deaths (ten *vs* nine) and morbid cardiovascular events (25 *vs* 34) were similar in the treated and untreated subjects. The initial report on the Oslo Study revealed that coronary events were more frequent in the treated group than in the control group (20 *vs* 13) although this was not significant; this raised anxieties about the possible adverse cardiac effects of thiazide diuretics. These concerns were reinforced when the 10 year follow-up was reported (Leren & Helgeland, 1986); 14 deaths due to coronary heart disease were found in the actively treated group *vs* only three in the untreated ($P < 0.01$).

The trials conducted up to 1984 thus suggested that there was distinct benefit from antihypertensive treatment in adults whose Vth phase diastolic pressure remained at or above 95 mm Hg over a period of observation. Numerically, the advantages were modest in the lower reaches of pressure and controversial in the diastolic range 90–95 mm Hg. Evidence of a protective effect in women was more slender. Better protection was apparent with better blood pressure control. There was no good evidence of prevention of coronary disease.

The 1985 trials

The three trials published in 1985 were the Medical Research Council (MRC) Trial of Treatment of Mild Hypertension (Medical Research Council Working Party 1985), the International Prospective Primary Prevention Study in Hypertension (IPPPSH) (The IPPPSH Collaborative Group 1985) and the European Working Party on High Blood Pressure in the Elderly (EWPHE) trial (Amery *et al.*, 1985). All aimed to illuminate previously obscure aspects of the treatment of mild hypertension. It was, in the event, disconcerting to find a factual error in the introduction to each paper.

The MRC trial

Aims

The declared main objective was to determine whether drug treatment of mild hypertension (Vth phase diastolic pressure in the range 90–109 mm Hg) reduced the incidence of strokes, deaths due to hypertension and coronary events in men and women aged 35–64 years. Subsidiary aims were to compare the course of blood pressure in two groups, one taking bendrofluazide and one taking propranolol, and to examine the adverse effects caused by these drugs.

Methods

The study was based largely on general practice. Patients were mainly from higher socio-economic groups. Subjects entered totalled 17,353, and 85,572 patient-years of observation were accumulated. Screening pressure was defined as the mean of four readings, taken on two separate occasions, showing diastolic pressure (Vth phase) in the range 90–109 mm Hg, with systolic pressure below 200 mm Hg. Entry to the trial was confirmed by the average of two later readings in the same range.

Patients were randomly allocated at entry to bendrofluazide 10 mg daily (or matching placebo), or to propranolol, which could be titrated up to 240 mg daily (or matching placebo). Target blood pressure for those randomized to active treatment was a diastolic pressure below 90 mm Hg, to be achieved within 6 months of entry. Supplementary treatment was added if control was inadequate. Initially, methyl dopa was added to bendrofluazide and guanethidine to propranolol; later, methyl dopa was used whatever the primary drug. The two primary drugs could also be employed in combination. The trial was single-blind only, since it was judged unreasonable to ask practitioners to participate in a study of this kind double-blind. Patients taking placebo whose blood pressure rose to 210 mm Hg systolic or 115 mm Hg diastolic (later reduced to 200 and 110 mm Hg, respectively) were transferred to the corresponding active drug. If patients on active treatment reached pressures at these levels the doctors were free to use whatever antihypertensive agents they wished. Development of severe hypertension as defined here was not taken as a trial end-point. Terminating occurrences included fatal or non-fatal stroke, coronary events, including both fatal and non-fatal myocardial infarction, sudden death thought to be a result of coronary artery disease, death due to hypertensive cardiac or renal disease or to rupture or

dissection of aortic aneurysm, and death from any other cause.

Statistical analysis

The results presented in the initial analysis are based on the groups at randomization, that is, as if the patient was still in the treatment group to which he or she was first allotted, even though substantial numbers were withdrawn, or given supplementary or alternative therapy.

Results

Blood pressure values An aspect which diminished the expected statistical power of the trial was that average blood pressure fell immediately after entry in all groups including those taking placebo. The fall was steepest in the first 2 weeks and continued more gradually for about 3 months. Thereafter, average pressure changed little. Subsequent annual measurements showed that between one-third and one-half of all those taking placebo had diastolic pressures below 90 mm Hg. Thus the trial actually examined high blood pressure of less severity than required by the initial design. A converse problem which also confounded the later analysis was that a cumulative 19% of men and 14% of women were withdrawn from placebo and commenced on active therapy because their blood pressure exceeded the trial range.

Supplementary therapy Thirty-four per cent of men and 24% of women initially allocated to bendrofluazide took supplementary antihypertensive therapy. The corresponding figures for those initially randomized to propranolol were 25 and 19%. In 5% of patients the two primary drugs were employed in combination.

Effects of treatment Stroke event rate was significantly reduced in those randomized to receive active treatment (60 vs 109 in the placebo group; $P = 0.006$). Cardiovascular events of all kinds were significantly fewer in the actively treated group (286 vs 352; $P = 0.01$). However, although coronary events dominated in this group, considerably exceeding the number of strokes, coronary event rate considered in isolation was not significantly different in the actively treated and placebo groups (222 and 234, respectively). When cardiovascular events of all kinds were considered, active treatment was seen to be significantly more effective in non-smokers than in smokers ($P < 0.05$). Deaths from all causes were similarly frequent in the actively treated (248) and placebo (253) groups. However, the

pattern was different in men, who appeared to gain protection from active treatment (157 vs 181 on placebo) compared with women, who fared better on placebo (91 vs 72). The difference between the sexes in this respect was significant ($P = 0.05$).

Blood pressure and cardiovascular risk Systolic pressure at entry was significantly associated with the risk of stroke, coronary events, all cardiovascular events and mortality from all causes. Diastolic pressure at entry was less closely related to the risk of subsequent events. The systolic pressure in the 6th month of the trial was significantly related to the subsequent development of stroke in both treatment and placebo groups, of coronary events in the placebo group, of all cardiovascular events in the propranolol and placebo groups, and of mortality from all causes in the placebo group. Diastolic pressure at 6 months was less clearly related to subsequent adverse events.

Comparison of benefits from propranolol and bendrofluazide Comparison of the primary forms of treatment was confounded by withdrawals, the addition of supplementary therapy and the combining of thiazide with propranolol. Supplementary drugs were added more often to bendrofluazide, although this group then achieved more effective blood pressure control. With these important reservations, it was seen that both drugs were associated with reduced rates of stroke (0.8/1000 patient-years on bendrofluazide, 1.9 on propranolol and 2.6 on placebo). The reduction in strokes on bendrofluazide was significantly greater than that on propranolol ($P = 0.002$). Habitual smoking did not affect the response to bendrofluazide but did appear to influence that to propranolol. For stroke the event rate was lower in smokers and non-smokers on bendrofluazide but only in non-smokers on propranolol. The difference between the drugs was significant ($P = 0.03$). Coronary event rate was not influenced by treatment in women, in male smokers or non-smokers on bendrofluazide, or in male smokers on propranolol. However, the rate in male non-smokers on propranolol was lowered substantially, from a rate of 7.5 to 5.0 per 1000 patient-years of observation.

Withdrawals and side effects The total cumulative percentages of men who stopped taking the treatment to which they were allocated, including those withdrawn from their randomized regimen who continued to be followed and those lapsing from the trial, were 43% of the bendrofluazide groups; 42% of the propranolol group and 47%

of the placebo group. Corresponding figures for women were 33, 40 and 40% respectively.

It is relevant to mention here an earlier report (Medical Research Council Working Party, 1981) on a subset of the MRC trial patients. The subset comprised 3725 men and 3504 women who at the time of evaluation remained only on their randomly allocated active treatment (bendrofluazide or propranolol) plus 3788 men and 3441 women taking placebo. Those requiring supplementary therapy were excluded from consideration. This subset analysis therefore permits clearer appreciation of the side effects of the primary drugs than does the main trial report.

The principal reasons for withdrawal from randomized treatment (numbers per 1000 patient-years) in men taking bendrofluazide were: impotence, 29; gout, 12; impaired glucose tolerance, 9; nausea, dizziness or headache, 9; lethargy, 7; constipation, 2. In women on bendrofluazide the figures were: nausea, dizziness or headache, 16; impaired glucose tolerance, 6; lethargy, 2; constipation, 2.

For men on propranolol, reasons given for withdrawal from treatment were: lethargy, 10; dyspnoea, 8; nausea, dizziness or headache, 7; impotence, 5; Raynaud's phenomenon, 5. Corresponding figures for women on propranolol were: lethargy, 15; nausea, dizziness or headache, 14; dyspnoea, 6; Raynaud's phenomenon, 6; cutaneous disorders, 2.

All of the events cited occurred significantly more often than in those on placebo, emphasizing that both the primary active drugs carried a substantial burden of side effects. The remarkably high frequency of male sexual impotence on bendrofluazide deserves special emphasis.

Another substudy (Medical Research Council Working Party, 1983) of the MRC trial examined the effect of bendrofluazide on ventricular ectopic activity, assessed by 24-h ambulatory electrocardiographic monitoring. Bendrofluazide treatment lasting 9–10 weeks was not associated with a significant increase in ventricular ectopic activity. However, patients treated with thiazide for an average of 2 years did show a significant excess of ventricular ectopy ($P = 0.025$), including complex forms such as multiform extrasystoles, couplets, R-on-T and bigeminy. Pooled data from both parts of this substudy showed a weak but highly significant correlation between the frequency of ventricular extrasystoles and serum potassium concentration ($r = -0.185$, $P = 0.003$). However, the correlation with serum urate was nearly as close ($r = 0.178$, $P = 0.004$) and the authors considered the explanation of the increased ventricular electrical activity to be uncertain.

The latter negative interpretation of the results has been criticized (Poole-Wilson, 1983) as 'curious and inappropriate', and regarded as 'equally compatible with, and (providing) evidence for, the view that hypokalaemia induced by thiazides was an important factor in the initiation of ventricular extrasystoles'.

No comparable study of the effect of propranolol on ventricular ectopy was conducted.

Comments on the MRC trial

The preamble to the report on the MRC trial (Medical Research Council Working Party, 1985) opens by rightly paying tribute to the pioneering work of Hamilton and his colleagues in 1964, an important but sometimes neglected study. However, it is incorrectly stated that Hamilton *et al.* examined patients with IVth phase diastolic pressures of 115 mm Hg and upwards. In fact, Hamilton's trial dealt with patients who had a IVth phase diastolic pressure of 110 mm Hg and above. As the Vth phase diastolic pressures of at least a proportion would therefore have been lower than 110 mm Hg, some of their patients would have had mild hypertension according to the range of the MRC trial.

The organization of the MRC study meant that a substantial majority of patients were recruited from higher socio-economic groups, a bias which could limit the applicability of the results.

Because of ethical considerations, 1011 people allocated randomly to placebo who developed blood pressures above the mild range defined were started on active therapy. These were the trial subjects most likely to sustain complications of hypertension. Moreover, they were later evaluated statistically as though they had remained on placebo. While the constraints leading to this action are understandable, there can be little doubt that the manoeuvre considerably weakened the statistical power of the trial, albeit to an extent which cannot now be determined. At the very least, these subjects ought to be regarded as having reached a trial end-point, even if not a morbid event, and counted accordingly. It was unwise in these circumstances to conclude (Medical Research Council Working Party, 1985): 'If 850 mildly hypertensive patients are given active antihypertensive drugs for 1 year, about 1 stroke will be prevented'. Therapy must surely have been substantially more beneficial than that, although the magnitude of the benefit cannot be accurately assessed. If this is denied, there was little justification for the manoeuvre of transferring these 1011 patients from placebo to treatment. The statistical power

of the trial was further weakened by the fall in diastolic pressure to below 90 mm Hg in one-third to one-half of subjects taking placebo.

The statistical approach in the MRC trial report appears to have been excessively cautious. This is evident from the reluctance to consider smokers and non-smokers separately on the grounds that the intention to do so had not been declared at the outset. The differential cardiovascular hazards in smokers are surely widely enough known for a separate scrutiny to be made even in the absence of a prior declaration. While it is reassuring in one sense to find statistical proprieties being strictly observed, on the other hand the reader has the uneasy feeling that a less inhibited analysis of the data could have brought forward important, but currently latent, observations.

The trial is in my opinion inconclusive, at least on the evidence so far presented (Medical Research Council Working Party, 1985), in assessing possible differential risks and benefits of thiazides versus β -adrenoceptor blockers. In the course of the study, the primary allocation was so contaminated by additional treatment and by transfer of patients between groups that a comparison of the two primary drugs must be approached with extreme caution. Furthermore, while blood pressure control was better in those initially allocated to thiazide, supplementary therapy was also more extensively employed in this group. Therefore, the simple conclusion that bendroflumazide was more effective than propranolol in preventing stroke requires qualification.

Although thiazide diuretics have undoubted benefits, a crucial issue, which was one of the principal objects of attention of the MRC trial, was whether they might also have adverse effects, especially in relation to cardiac events. In particular, it had been suspected (Robertson, 1978, 1983a,b, 1984, 1986; Poole-Wilson, 1983) that by diminishing serum and total body potassium and serum magnesium, diuretic therapy might predispose to ventricular arrhythmias and so enhance the risk of sudden death in hypertensive patients with coronary artery disease. It should be emphasized that the suggestion was not that thiazides were wholly bad, but that their undoubted benefits might be partly offset by some adverse aspects of their action.

The well controlled substudy (Medical Research Council Working Party, 1983) of the MRC trial discussed above provided evidence in support of that hypothesis, that patients on thiazide alone showed excess ventricular ectopic activity, often complex in form, on 24 h ambulatory electrocardiographic monitoring. It remains,

of course, uncertain whether such ventricular ectopic activity carries an adverse prognosis. Nevertheless, the observations must continue to call into question the safety of thiazide treatment.

The present report (Medical Research Council Working Party, 1985) on the MRC trial does little to illuminate this problem further. Thiazide usage, as in earlier studies, was not associated with a reduction in deaths from coronary disease and the data presented are entirely consistent with the possibility that thiazide diuretics, when used in the treatment of hypertension, might be partly beneficial and partly adverse. The original concern thus remains, and it is surprising to find normally perceptive critics regarding the MRC trial as 'rehabilitating diuretics' (Beever, 1986) and putting 'an end to unwarranted speculation on the supposed dangers of diuretic treatment' (Ramsay, 1985). Worries about the possible cardiac risks of diuretics may be ill-founded, but in my opinion and that of some other writers (Poole-Wilson, 1983) they are not dispelled by the data presented.

One exciting finding to emerge was that propranolol was associated with a reduction of coronary events in non-smoking men. The authors are, however, rightly cautious. These results raise possibilities which deserve, and will surely receive, attention in a prospective study.

IPPPSH

Aims

The principal aim of IPPPSH (the IPPPSH Collaborative Group, 1985) was to examine whether the incidence of adverse cardiac and cerebrovascular events could be influenced by the treatment of hypertension with a β -adrenoceptor blocking agent. Oxprenolol was the drug selected for study.

Methods

Altogether, 6357 men and women aged 40–64 years, with Vth phase diastolic pressure of 110–125 mm Hg, were included. Roughly half were not on therapy on entry; the others were receiving antihypertensive drugs. In the trial, patients were randomly assigned double-blind to slow-release oxprenolol 160 mg daily or matching placebo. Study medication could be increased or antihypertensive drugs other than β -adrenoceptor blockers might be added in either group with the aim of reducing diastolic pressure to 95 mm Hg or less. Critical events were sudden cardiac death, fatal or non-fatal myocardial infarction and cerebrovascular accident.

Statistical analyses were based on the intention-to-treat principle, that is, on the group to which each patient was initially assigned.

Results

Medication During the study and while on double-blind treatment, 30% of the patients received oxprenolol only and 15% placebo. Total diuretic use was 67% in the oxprenolol group and 82% in the non β -adrenoceptor blocker based group. A third drug (sympatholytic and/or vasodilator) was used in 33% of the oxprenolol group and in 48% of the non β -adrenoceptor group.

Blood pressure control Blood pressure control was significantly better in those patients who received oxprenolol than in those who did not (average 143.6/88.9 vs 147.4/90.1 mm Hg; $P < 0.001$).

Effect of treatment on complication rate Despite the better blood pressure control in those on oxprenolol, sudden deaths, myocardial infarction and cerebrovascular accidents were similarly frequent, whether or not oxprenolol was taken. However, evidence was obtained of an interaction between β -adrenoceptor blockade and smoking in men. Critical cardiac events were only half as frequent in male non-smokers who took the β -adrenoceptor blocker as in those who did not (5.4 vs 11.6 per 1000 patient-years). This finding was remarkably similar to the beneficial effect observed in non-smoking men taking propranolol in the MRC trial (Medical Research Council Working Party, 1985). However, in IPPPSH the opposite tendency, to an increased rate of cardiac events, was seen in male smokers taking oxprenolol (rate 18.1 vs 14.5 per 1000 patient-years).

Blood pressure and cardiovascular risk A very clear and important finding in IPPPSH was that the frequencies of cardiac events (myocardial infarction and sudden death) and strokes were correlated with the diastolic blood pressure achieved in the course of the study. The slope of the correlation showing relative risk was steeper for stroke than for cardiac events. This is a consistent aspect repeatedly demonstrated previously in trials of hypertensive treatment, that such therapy prevents stroke more effectively than coronary attacks. The IPPPSH findings thus suggest that the treatment of hypertension may reduce myocardial infarction and sudden death as well as stroke. However, this is not established by the data; it is in theory possible

that those less prone to coronary events have more readily controlled hypertension (Newman & Robertson, 1959), while the two features may not be causally related. Alternatively, we might theoretically be observing the well-known relationship between arterial pressure and adverse events, in a group of patients on antihypertensive therapy which could be largely irrelevant. The findings nonetheless suggest that blood pressure reduction should be as effective as possible, perhaps down to a Vth phase diastolic pressure of 85 mm Hg.

Comments on IPPPSH

The main aim of IPPPSH was to examine the proposition that β -adrenoceptor blockade might carry especial benefits in the treatment of hypertension. A particular hope was that these agents might protect against coronary events (Robertson, 1978), a hope that was encouraged by their undoubted success when given after myocardial infarction (Robertson, 1983b; Norwegian Multi-center Study Group, 1981; Beta-Blocker Heart Attack Study Group, 1981; Hjalmarson *et al.*, 1981; Editorial, 1982; Hampton, 1981). It was in this connection disconcerting to read in the introduction to the report (The IPPPSH Collaborative Group, 1985) that a major reason for selecting oxprenolol for evaluation was an earlier successful postinfarction study (Taylor *et al.*, 1982) using that drug. The outcome of that earlier trial was a good deal less clear than the authors of IPPPSH imply; there was no overall difference in either mortality or cardiac events between the placebo and oxprenolol groups. If this was indeed a major reason for selecting oxprenolol in the IPPPSH trial (and the statement is repeated in the discussion) the argument eludes the present writer.

The design of IPPPSH hampered testing on the primary hypothesis. Half of all the patients entered were already on antihypertensive drugs of various kinds and had been for an unspecified time. This might well have modified the outcome. Furthermore, in the course of the study, over 60% of all those allocated to oxprenolol were also given a diuretic, concurrently in many cases with one or more of an assortment of other agents. Since a hypothesis (Robertson, 1978) closely linked with the main aim of IPPPSH was that thiazides may have some undesirable cardiac effects in hypertensive patients—a hypothesis, it should be emphasized, that remains unsubstantiated—it is curious that the study design was clouded in this way. Any such adverse effects of diuretics could well have obscured possible benefits of oxprenolol. The extenuation offered

by the authors, that the trial circumstances reflected everyday clinical practice, is more suppletory than convincing. Real life, in all its confusion, can readily be observed at any time. Trials should be designed as far as possible to isolate and focus on the issue under study, all other aspects being controlled.

A further criticism voiced (Cruikshank, 1985), and not fully answered, is that once-daily dosing with oxprenolol possibly did not provide effective blood pressure control over 24 h.

In IPPPSH, there was a strong suggestion of a protective effect of oxprenolol against coronary attacks in male non-smokers. A converse, and less encouraging, observation was that oxprenolol was accompanied by more frequent coronary events in men who smoked. It must be emphasized that this latter aspect is not established with certainty. It could be a feature of non-selective rather than selective β -adrenoceptor blockade. Cigarette smoking has been shown to be acutely pressor in subjects taking non-selective β -adrenoceptor blocking drugs, while this is not so with cardioselective agents such as atenolol (Trap-Jensen *et al.*, 1979). A range of possibilities of great clinical potential has thus been raised.

EWPHE

Aims

The EWPHE trial (Amery *et al.*, 1985) was designed to assess the effect of antihypertensive drug therapy in patients over 60 years old.

Methods

Eight hundred and forty men and women over 60 years old, with a systolic pressure in the range 160–239 mm Hg and a diastolic pressure in the range 90–119 mm Hg, were randomized double-blind to receive active treatment (hydrochlorothiazide plus triamterene) or matching placebo. If the blood pressure remained elevated, methyl-dopa was added to the active regimen or matching placebo in the placebo group. Specific study-terminating events included death, non-fatal cerebral or subarachnoid haemorrhage, development of bilateral retinal haemorrhages and/or exudates and/or papilloedema, dissecting aortic aneurysm, congestive heart failure not controlled by diuretics or antihypertensive drugs, hypertensive encephalopathy, severe increase in left ventricular hypertrophy, and rise in blood pressure exceeding the defined limits. An overall intention-to-treat analysis was confined to mortality. A more detailed evaluation was performed on the double-blind part of the trial.

Results

Blood pressure control Active antihypertensive therapy was accompanied by a highly significant and sustained reduction in systolic and diastolic blood pressures.

Effect of treatment on complication rate The intention-to-treat analysis showed a non-significant change in total mortality rate (-9%). There was, however, a significant reduction in cardiovascular mortality (-27% , $P = 0.037$) made up of a significant decrease in cardiac mortality (-38% , $P = 0.036$) and an insignificant decrease in cerebrovascular mortality (-32% , $P = 0.16$). Similarly, total mortality rate was not significantly affected by treatment in the double-blind part of the trial (-26% , $P = 0.077$). There was an insignificant decrease in cerebrovascular mortality on treatment (-43% , $P = 0.15$). The number of cardiac deaths was significantly lower in those on active treatment double-blind (-47% , $P = 0.048$), and this included a substantial reduction in deaths from myocardial infarction (-60% , $P = 0.043$). Against this, non-fatal myocardial infarction tended to be more frequent in the treated group. Active treatment also reduced the incidence of severe, but not mild, congestive heart failure, suggesting to the authors that treatment did not affect the myocardial disease leading to cardiac failure but reduced its severity by lowering left ventricular work.

Side effects The benefits were offset in those on active therapy by a decrease in glucose tolerance and increase in serum uric acid and creatinine, and an insignificantly increased frequency of bone fractures (Amery, 1985).

Comments on the EWPHE trial

The EWPHE trial report begins by stating that there was previously little evidence (and that was statistically insignificant) of the benefit of treating hypertension in subjects over 60 years old. This statement is rather unkind to the Australian study of 1981 (Australian Therapeutic Trial in Mild Hypertension, 1981), which examined 594 patients over 60 years old at entry. In the Australian trial there was a significant reduction ($P < 0.025$) in the number of end-points in those randomly allocated to active antihypertensive therapy as against placebo. As these elderly subjects formed part of the larger Australian treatment trial (Australian Therapeutic Trial in Mild Hypertension, 1980), and as the intention to scrutinize those aged over 60

when the trial was started was not declared, it might be argued that the statistical precision was accordingly weakened. This argument has some force, but it does not justify wholesale dismissal of the earlier Australian report.

The EWPHE trial is disappointing since, despite the participation of 18 centres over 12 years, only 840 patients were randomized. Thus all those aged over 60 were grouped together and we are told simply that the mean age ($\pm$ s.d.) at entry was 72 ± 8 years. Nevertheless, important data were obtained on the benefits and risks of antihypertensive treatment in the elderly. In particular, the trial breaks new ground in demonstrating a significant reduction in deaths from myocardial infarction.

General observations on the 1985 trials

The MRC trial

The publication of this trial report has excited many comments, some odder than others. One of the more outspoken comes from Beevers (1986), previously a stern critic of the earlier American HDFP study (Beevers, 1982, 1983). Beevers, who himself participated in the MRC trial, was apparently so dismayed by its outcome (which he described as a 'damp squib') that he regarded it as vindicating 'even the extraordinary HDFP'. Comprehension of how the inadequacies of one study can remedy defects in another requires mental agility not possessed by the present writer. Despite the disappointments, the MRC trial did confirm the benefits to be derived from treating very mild hypertension. Further, the numerical advantage of active therapy was greater than was alleged by the authors of the report because, firstly, over 1000 of the patients most at risk and allocated to placebo were effectively lost to analysis, and secondly, a substantial number of subjects on placebo settled to blood pressures below the range it was intended to study. Less evidence of benefit was seen in women. Treatment did reduce coronary events, but only in non-smoking men on propranolol.

Both bendrofluazide and propranolol were associated with a substantial burden of side effects at the dosage employed (Medical Research Council Working Party, 1981). Unlike the authors of the trial report (Medical Research Council Working Party, 1985) and some other commentators (Ramsay, 1985; Beevers, 1986), I do not find that the data dispel concerns about the possible risks of long-term thiazide treatment.

A less inhibited analysis than has been provided so far could be valuable. In particular, an appre-

ciation of in-trial systolic and diastolic pressures in both men and women in relation to stroke and coronary events, especially in patients receiving only propranolol, only bendrofluazide, and only placebo, would be most interesting. Many of these points will very probably be clarified in future reports (Lever, personal communication).

IPPPSH

IPPPSH revealed no special benefit from the use of a β -adrenoceptor blocker in treating hypertension, except, as in the MRC trial, in limiting coronary events in male non-smokers. However, the design could have obscured advantages of β -adrenoceptor blockade, advantages which might be revealed in a cleaner study. The trial indicated the improved prognosis associated with thorough blood pressure reduction, with lower blood pressures being accompanied by progressively lower attack rates from both stroke and cardiovascular events, although the effect was clearer for stroke than for heart attack.

EWPHE

The EWPHE report confirmed the protective effect of antihypertensive therapy in those over 60 years old, although at the price of a substantial burden of side effects. It was especially encouraging that even when treatment was based on a thiazide diuretic, with added triamterene, fatal (but not non-fatal) myocardial infarctions were significantly reduced in frequency.

Other studies: hypertension treatment in practice

Three other studies are relevant here because they carry implications for future practice. They have been reviewed in more detail elsewhere (Hansson & Robertson, 1987).

Lindholm (1984) examined the cardiovascular morbidity of treated hypertensives in the community of Dalby, near Lund in Sweden. Comparison was made with normal subjects of the same age and sex in the same population. In a number of age groups the treated hypertensives had significantly higher cerebrovascular and cardiovascular morbidity than did the matched normotensive subjects. Importantly, however, the treated patients also had on average significantly higher blood pressures than the controls.

Samuelsson reviewed the effects of antihypertensive therapy in 686 middle-aged hypertensive men in Gothenburg, Sweden (Samuelsson, 1985). As in the Dalby series, the incidence of cardiovascular complications, despite therapy, remained

above the normal rate (Hansson & Robertson, 1986).

A retrospective survey of the data of the Glasgow Blood Pressure Clinic revealed that the mortality rate, despite treatment, was 2–5 times higher than that in the two local reference populations (Isles *et al.*, 1986). Reduction of risk was however greatest in those whose blood pressure was most effectively lowered with treatment.

Several possible explanations for these rather disconcerting findings have been considered (Hansson & Robertson, 1987). First, long-standing hypertension causes cardiovascular changes which are only partially corrected by antihypertensive therapy. Second, as discussed above, some of the drugs used in the treatment of hypertension have potentially adverse metabolic effects which could partly offset the benefits resulting from blood pressure control. Third, and most important, blood pressure may not have been lowered enough to obviate risk.

Conclusions

The 1985 crop of trials answered fewer questions, and those less clearly, than had been hoped. Nevertheless, the effort and dedication devoted to the studies have been repaid by the data revealed. In retrospect, the lengthy advent of these difficult projects perhaps generated excessive optimism and expectations. Despite the reservations, the findings have spawned important new hypotheses which should be tested in prospective studies.

However, at least five major results have emerged from these trials. First, and unsurprisingly, antihypertensive therapy must be linked with efforts to discourage cigarette smoking. Second, blood pressure reduction should be as thorough as possible. Third, there is now some evidence, though it remains tenuous and requires confirmation, that coronary events can be limited by antihypertensive therapy, although not so readily as can strokes. Fourth, we require antihypertensive agents which are tolerated better than those employed in the trials reviewed here. Fifth, and most important, while the stepped-care approach (Moser, 1983; Gross & Robertson, 1979) has given valuable service, its day should now be over. In future, each patient, his risks, potential benefits and response to treatment, must be treated individually.

This article is a modified and partially condensed version of one which appears in the Yearbook of Hypertension, 1986, edited by L. Hanssen. Parts are reproduced here by kind permission of the Editor and the publishers, Gower Press, London.

References

- Amery, A. (1985). Discussion after the presentation of the results of the European Working Party on High Blood Pressure in the Elderly (EWPHE). *J. Hypertension*, **3** (suppl. 3), S509-S511.
- Amery, A., Birkenhäger, W., Brixko, P., Bulpitt, C., Clement, D., Deruyttere, M., De Schaepestryver, A., Dollery, C., Fagard, R., Forette, F., Forte, J., Hamdy, R., Henry, J. F., Joossens, J. V., Leonetti, G., Lund-Johansen, P., O'Malley, K., Petrie, J., Strasser, T., Tuomilehto, J. & Williams, B. (1985). Mortality and morbidity results from the European Working Party on High Blood Pressure in the Elderly Trial. *Lancet*, **i**, 1349-1355.
- Australian Therapeutic Trial in Mild Hypertension (1979). Initial results. *Clin. Sci.*, **57** (suppl. 5), 449-452.
- Australian Therapeutic Trial in Mild Hypertension (1980). Report by the management committee. *Lancet*, **i**, 1261-1267.
- Australian Therapeutic Trial in Mild Hypertension (1981). Treatment of mild hypertension in the elderly. *Med. J. Aust.*, **2**, 398-402.
- Beevers, D. G. (1982). The HDFP controversy: plenty of data but not much information. *Cardiol. Today*, **10**, 1-2.
- Beevers, D. G. (1983). Risks of hypertension and benefits of treatment. In *Handbook of Hypertension*, Vol. 1. Clinical Aspects of Essential Hypertension, ed. Robertson, J. I. S., pp. 378-396. Amsterdam: Elsevier.
- Beevers, D. G. (1986). MRC trial of hypertension treatment. *Cardiol. Today*, **14**, 4-5.
- Berglund, G., Wilhelmsen, L., Sannerstedt, R., Hansson, L., Andersson, D. & Sivertsson, R. (1978). Coronary heart disease after treatment of hypertension. *Lancet*, **i**, 1-5.
- Beta-blocker heart attack study group (1981). The beta-blocker heart attack trial. *J. Am. med. Ass.*, **246**, 2073-2074.
- Cruikshank, J. M. (1985). Discussion after the presentation of the results of the International Prospective Primary Prevention Study in Hypertension (IPPPSH). *J. Hypertension*, **3** (suppl. 3), S517-S518.
- Editorial (1982). Long-term and short-term beta-blockade after myocardial infarction. *Lancet*, **i**, 1159-1161.
- Freis, E. D. (1982). Should mild hypertension be treated? *New Engl. J. Med.*, **307**, 306-309.
- Gross, F. & Robertson, J. I. S. (1979). (eds). *Arterial hypertension*. London: Pitman Medical.
- Hamilton, M., Thompson, E. N. & Wisniewski, T. K. M. (1964). The role of blood pressure control in preventing complications of hypertension. *Lancet*, **i**, 235-238.
- Hampton, J. R. (1981). The use of beta-blockers for the reduction of mortality after myocardial infarction. *Eur. Heart J.*, **2**, 259-268.
- Hampton, J. R. (1983). An appraisal of hypertension trials. *Medicographia*, **5** (suppl. 2), 12-15.
- Hampton, J. R. (1984). Doubts about hypertension. *Cardiol. Today*, **12**, 4.
- Hansson, L. & Robertson, J. I. S. (1987). Is hypertension treated adequately? *Drugs* (in press).
- Helgeland, A. (1980). Treatment of mild hypertension: a 5-year controlled drug trial. The Oslo Study. *Am. J. Med.*, **69**, 725-732.
- Hjalmarson, A., Elmfeldt, D., Herlitz, J., Holmberg, S., Malek, I. & Nyberg, G. (1981). Effect on mortality of metoprolol in acute myocardial infarction. *Lancet*, **ii**, 823-827.
- Hypertension Detection and Follow-up Program Cooperative Group (1979a). Five-year findings of the Hypertension Detection and Follow-up Program. 1. Reduction in mortality of persons with high blood pressure, including mild hypertension. *J. Am. med. Ass.*, **242**, 2562-2571.
- Hypertension Detection and Follow-up Program Cooperative Group (1979b). Five-year findings of the Hypertension Detection and Follow-up Program. II. Mortality by race, sex and age. *J. Am. med. Ass.*, **242**, 2372-2377.
- Hypertension Detection and Follow-up Program Cooperative Group (1982). The effect of treatment on mortality in 'mild' hypertension. *New Engl. J. Med.*, **307**, 976-980.
- Isles, C. G., Walker, L., Beevers, D. G., Brown, I., Cameron, H., Clarke, J., Hawthorne, V., Hole, D., Lever, A. F., Robertson, J. W. K. & Wapshaw, J. A. (1986). Mortality in patients of the Glasgow Blood Pressure Clinic. *J. Hypertension*, **4**, 141-156.
- Leren, P. & Helgeland, A. (1986). Oslo hypertension study. *Drugs*, **31** (suppl. 1), 41-45.
- Lindholm, L. (1984). *Hypertension and its risks: epidemiological studies in Swedish primary health care*. Ph.D. Thesis, University of Lund.
- Maxwell, M. H. (1982). The HDFP controversy: not a strange study. *Cardiol. Today*, **10**, 1-2.
- McFate-Smith, W. (1977). Treatment of mild hypertension. Results of a 10-year intervention trial. US Public Health Service Hospitals Study Group. *Circ. Res.*, **40** (suppl. 1), 98-105.
- Medical Research Council Working Party (1981). Adverse reactions to bendrofluzide and propranolol following treatment of mild hypertension. *Lancet*, **ii**, 539-543.
- Medical Research Council Working Party (1983). Ventricular extrasystoles during thiazide treatment: substudy of MRC Mild Hypertension Trial. *Br. med. J.*, **287**, 1249-1253.
- Medical Research Council Working Party (1985). MRC Trial of treatment of mild hypertension: principal results. *Br. med. J.*, **291**, 97-104.
- Moser, M. (1983). A decade of progress in the management of hypertension. *Hypertension*, **5**, 808-813.
- Moser, M. (1985). The case for treating hypertension. *Cardiol. Today*, **13**, 5.
- Moser, M. & Gifford, R. W. (1985). Why less severe degrees of hypertension should be treated. *J. Hypertension*, **3**, 437-447.
- Newman, M. J. D. & Robertson, J. I. S. (1959). Some aspects of prognosis in treated hypertension. *Br. med. J.*, **1**, 1368-1373.
- Norwegian Multicenter Study Group (1981). Timolol-

- induced reduction in mortality and reinfarction in patients surviving acute myocardial infarction. *New Engl. J. Med.*, **394**, 801–807.
- Pickering, G. W. (1961). *The Nature of Essential Hypertension*. London: Churchill.
- Poole-Wilson, P. A. (1983). Ventricular extrasystoles during thiazide treatment. *Br. med. J.*, **287**, 1798–1799.
- Ramsay, L. E. (1985). Mild hypertension: treat patients, not populations. *J. Hypertension*, **3**, 449–455.
- Robertson, J. I. S. (1978). Complications of mild hypertension. *Ann. N.Y. Acad. Sci.*, **304**, 64–65.
- Robertson, J. I. S. (1983a). Hypertension: primary and secondary prevention. In *Preventive Cardiology*, ed. Julian, D. G. & O'Neal Humphries, J., pp. 62–85. London: Butterworths.
- Robertson, J. I. S. (1983b). Concluding remarks: cum grano salis. In *Mild Hypertension: Recent Advances*, ed. Gross, F. & Strasser, T., pp. 413–418. New York: Raven Press.
- Robertson, J. I. S. (1984). The risk-benefit equation: when to initiate treatment. *Br. J. clin. Pharmac.*, **18**, 181S–185S.
- Robertson, J. I. S. (1987). Essential Hypertension: a critical point of view. *J. cardiovasc. Pharmac.* (in press).
- Samuelsson, O. (1985). Hypertension in middle-aged men. *Acta med. Scand.* (Suppl. 702), 1–79.
- Swales, J. D. (1985). *Platt versus Pickering: an Episode in Recent Medical History*. London: The Keynes Press/British Medical Association.
- Taylor, S. H., Silke, B., Ebbutt, A., Sutton, G. C., Prout, B. J. & Burley, D. M. (1982). A long-term prevention study with oxprenolol in coronary heart disease. *New Engl. J. Med.*, **307**, 1293–1301.
- The IPPPSH Collaborative Group (1985). Cardiovascular risk and risk factors in a randomized trial of treatment based on the beta-blocker oxprenolol: the International Prospective Primary Prevention Study in Hypertension (IPPPSH). *J. Hypertension*, **3**, 379–392.
- Toth, P. J. & Horwitz, R. I. (1983). Conflicting clinical trials and the uncertainty of treating mild hypertension. *Am. J. Med.*, **75**, 482–487.
- Trap-Jensen, J., Carlsen, J. E., Svendsen, T. L. & Christensen, N. J. (1979). Cardiovascular and adrenergic effects of cigarette smoking during immediate non-selective and selective beta-adrenoceptor blockade in humans. *Eur. J. clin. Invest.*, **9**, 181–189.
- Veterans Administration Cooperative Study Group on Antihypertensive Agents (1967). Effects of treatment on morbidity in hypertension. Results in patients with diastolic blood pressures averaging 115 through 129 mm Hg. *J. Am. med. Ass.*, **202**, 1028–1034.
- Veterans Administration Cooperative Study Group on Antihypertensive Agents (1970). Effects of treatment on morbidity in hypertension. II. Results in patients with diastolic pressure averaging 90 through 114 mm Hg. *J. Am. med. Ass.*, **213**, 1143–1152.
- Veterans Administration Cooperative Study Group on Antihypertensive Agents (1972). Effect of treatment on morbidity in hypertension. III. Influence of age, diastolic pressure, prior cardiovascular disease; further analysis of side-effects. *Circulation*, **45**, 991–1004.