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Overview of Drugs in Arterial Thrombosis [and Discussion]

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Overview of drugs in arterial thrombosis

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The recent history of randomized controlled trials in the prevention of ischaemic heart disease (i.h.d.) is considered. In 1970, it seemed that little could be done to prevent recurrence of the disease and there was almost no information on the potential for preventing its onset. Over the past decade, this rather pessimistic view has changed to one of guarded optimism. Yet there are still no drug régimes that command general support. One reason for the inconclusive results of recent trials may have been the assumption that myocardial infarction and sudden death share the same pathology. Another reason is the diversity of pathogenetic mechanisms and prognoses in i.h.d. Many patients probably stand little chance of benefiting from a particular drug either because it affects mechanisms other than those responsible for their disease or because their prognosis, excellent or hopeless, is unlikely to be influenced whatever treatment they receive. It is consequently difficult to ensure reasonable chances of demonstrating benefits in those who may really stand to gain. A tendency for pharmacological information to become available during or after a large trial, rather than beforehand, has added to the difficulties. Despite all their problems, randomized controlled trials remain the only way of testing drugs for the prevention of arterial disease. Suggestions are made for increasing the chances of clear results in future trials and of reaching the stage of benefit demonstrated sufficiently convincingly to form a basis for clinical practice. These suggestions include the use of factorial designs enabling the evaluation of more than one drug in a particular trial and the development of methods for selecting homogeneous groups of patients.

1. Introduction

In 1970, it seemed that little could be done to prevent the recurrence (secondary prevention) of ischaemic heart disease (i.h.d.). Dietary intervention aimed at lowering blood cholesterol levels had proved ineffective (Medical Research Council 1968; Leren 1970). Several trials of anticoagulants had collectively suggested some benefit (International Anticoagulant Review Group 1970) though no trial on its own had done so convincingly. The uncertainty that followed these trials, together with the risks of bleeding and the need for continuous laboratory control of treatment, led to the abandonment of anticoagulants for routine management. The verdict on anticoagulants, however, was 'not proven' rather than 'proven of no value'; the question remains open and is considered again later in this paper.

Now, 10 years later, several other agents have been tested in secondary prevention trials and experience from primary prevention trials is also beginning to accumulate. By contrast with the situation a decade ago, many now believe that the prevention of i.h.d. by pharmacological means is possible. Yet there are still no specific drugs which command general support. Why is this?

This contribution reviews the developments that have changed the outlook for i.h.d. prevention from one of considerable pessimism to one of guarded optimism. It identifies some of the

difficulties that will have to be overcome in reaching the next stage – that of benefit demonstrated sufficiently clearly to form a basis for clinical practice. The paper cites several trials to exemplify different points, but it is not a comprehensive review of these trials. The main emphasis is on i.h.d., though the prevention of cerebrovascular disease is also considered.

2. Ischaemic heart disease: heterogeneity of manifestations, mechanisms and prognosis

(*a*) *Manifestations*

Terms such as ischaemic or coronary heart disease have for many years been used to include different clinical manifestations: sudden death, myocardial infarction and angina pectoris. At autopsy, advanced vessel wall disease is seen in most of those who die suddenly or after the established clinical features of myocardial infarction. But evidence of recent thrombosis and cardiac necrosis is found less often after sudden death than after myocardial infarction (Mitchell 1978). The interpretation of this observation is not straightforward (Meade 1981). The very intense fibrinolytic activity associated with sudden death could be enough to lyse thrombi responsible for a swift and catastrophic arrhythmic event. Platelet microthrombi may be responsible for sudden death (Haerem 1978). Explanations such as these – largely though not entirely conjectural – are compatible with a thrombotic explanation for sudden death as well as for myocardial infarction. But the two presentations should not be assumed to share exactly the same pathology. Besides morbid anatomical differences, there are differences in the apparent effects of drugs and of dietary changes on the occurrence of sudden death and myocardial infarction. The secondary prevention trials of aspirin have indicated a possible benefit against reinfarction. This contrasts with a less convincing effect against fatal events (mostly 'sudden') (*Lancet* 1980). The same contrast has been reported in a dietary trial (Turpeinen *et al.* 1979) and in the W.H.O. primary prevention trial of clofibrate (Committee of Principal Investigators 1978).

(*b*) *Mechanisms*

Table 1 summarizes the intended drug effects of the main i.h.d. trials so far reported.

The first five approaches are intended to prevent or diminish possible pathogenetic changes in the coronary circulation. The sixth deals with electrical and myocardial abnormalities. A feature of most of the secondary prevention trials has been their tendency to favour the active treatments (assuming that the drugs do indeed exert their benefits via the intended effects, a point considered again later). Although their results are far from conclusive, this tendency, together with evidence from other sources, suggests that all the mechanisms summarized in table 1 are involved in the pathogenesis of recurrent i.h.d. The same applies to the onset of first episodes of i.h.d., studied in primary prevention trials. Clofibrate reduced the incidence of non-fatal myocardial infarction by 25% (Committee of Principal Investigators 1978), though it had no effect on the incidence of fatal heart attacks or angina pectoris. A later report (Committee of Principal Investigators 1980) described the 25% higher mortality from all causes in the clofibrate treated group. The widespread use of clofibrate for the primary prevention of i.h.d. is thus contra-indicated. The beneficial effect of clofibrate on non-fatal infarction is, however, a valuable observation in terms of understanding the pathogenesis of this manifestation of i.h.d. Two primary prevention trials (referred to again in §5) have demonstrated reductions in the

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incidence of cardiovascular disease after the detection and treatment of hypertension (Hypertension Detection and Follow-up Program 1979; Australian Therapeutic Trial 1980). (Results of primary prevention trials of aspirin are awaited.)

Thus, quite apart from their clinical implications, the trials have emphasized the limitations of thinking of i.h.d. and its prevention in terms of single processes. There must be some people in whom one disorder is the leading cause of a first or recurrent clinical episode of i.h.d. But this disorder may be in lipid metabolism, in blood pressure control, in 'hypercoagulability' or in platelet sensitivity. In other people, combinations of disorders are probably responsible for subsequent events. There is, therefore, almost certainly a considerable diversity of pathogenetic mechanisms in i.h.d.

TABLE 1. PREVENTION OF ARTERIAL DISEASE, ESPECIALLY I.H.D.: INTENDED DRUG EFFECTS ON PATHOGENETIC MECHANISMS

1. Prevention of fibrin formation
2. Enhancement of fibrin dissolution
3. Prevention of platelet aggregation
4. Lowering of blood lipids
5. Lowering of blood pressure (principally for stroke prevention)
6. Prevention of arrhythmias

1. Secondary prevention	International Anticoagulant Review Group (1970)
	Sixty Plus Reinfarction Study (1980)
2. Secondary prevention	European Collaborative Study (1975)
	European Co-operative Study Group (1979)
3. Secondary prevention	Elwood *et al.* (1974)
	Elwood & Sweetnam (1979)
	Coronary Drug Project Research Group (1976)
	Anturane Reinfarction Trial (1978, 1980)
	Aspirin Myocardial Infarction Study Research Group (1980)
	Persantine–Aspirin Reinfarction Study Research Group (1980)
4. Primary prevention	Committee of Principal Investigators (1978, 1980)
Secondary prevention	Dewar & Oliver (1971) (and accompanying reports)
	Coronary Drug Project Research Group (1975)
	Rosenhamer & Carlson (1980)
5. Primary prevention (principally)	Veterans Administration (1967, 1970)
	Hypertension Detection and Follow-up Program (1979)
	Australian Therapeutic Trial (1980)
6. Secondary prevention	Wilhelmson *et al.* (1974)
	Multicentre International Study (1975, 1977)
	Baber *et al.* (1980)

The references are illustrative rather than comprehensive, especially for 1, 2 and 6.

(*c*) *Prognosis*

Many patients die soon after a myocardial infarct, whatever treatment they are given. On the other hand, many make a rapid recovery, also probably uninfluenced by treatment. There remains a proportion, of unknown size, in whom treatment may be able to alter the prognosis.

(*d*) *Implications*

The combined effects of differences in the manifestations, mechanisms and prognosis of i.h.d. mean that participants in preventive trials are likely to be heterogeneous in a number of important respects. But a drug with a specific action may only be capable of influencing one type

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of outcome (e.g. sudden death) in a relatively small proportion of patients. Thus i.h.d. prevention trials are subject to a low ratio of 'signal' to 'noise'.

The consequences of the heterogeneity of participants in trials vary according to whether these are of secondary or primary prevention.

Patients become eligible for secondary prevention trials because they have survived a myocardial infarction and not, other than exceptionally, because they can be shown to have had a particular disorder, such as hyperlipidaemia. Even on blood pressure, systematic pre-morbid information will usually be lacking. In addition, the infarct will itself lead to wide-ranging changes – in blood lipids (Dodds & Mills 1959), clotting factors (Meade 1981) and blood pressure – thus making it almost impossible retrospectively to assess the contribution of different processes to the event. Secondary prevention trials are therefore particularly susceptible to the consequences of the diversity of pathogenetic mechanisms in i.h.d. Entering patients into such a trial because they have had infarcts is rather like entering patients into a leukaemia chemotherapy trial without knowing the cell type. In either case, some of the patients stand to benefit. Many, however, do not, and their effect is to increase the difficulty of demonstrating benefit in those for whom the drug may indeed be useful.

Secondary prevention trials are also especially affected by the differences in prognosis referred to earlier. The number of patients required could be reduced, perhaps appreciably, if it were possible to exclude those likely to do very well or very badly, regardless of treatment. Some progress in this direction might be made through the prognostic value of electrocardiographic (e.c.g.) excercise testing shortly before discharge from hospital. Thus, the 1 year mortality in patients without S–T changes during exercise was 2.1%, compared with 27% in those with S–T segment depression (Théroux *et al.* 1979). This approach would mean screening large numbers of patients and would also preclude very early entry into a trial. On the other hand, those with a hopeless prognosis would have died by the time exercise testing was feasible. The test would then identify those at high risk but among whom treatment might make a substantial impact. Clinical e.c.g. details, blood pressure readings and chest X-ray findings were among measures used to predict outcome in the placebo group of the Coronary Drug Project (1974). In a 3 year follow-up period, 30.7% of the deaths took place in the 10% of patients at greatest risk. (Over 90% of the deaths were cardiovascular; 81.6% were due to i.h.d.) It is surprising that more use has not hitherto been made of readily available clinical information which might be used to select high-risk groups for secondary prevention trials.

From a statistical point of view, the higher mortality and recurrence rates in secondary than in primary prevention trials are, of course, an advantage, though even in secondary trials the magnitude of these rates is not enough to avoid the need for hundreds or even thousands of patients.

Primary prevention trials are carried out in participants who can often be selected according to the characteristic to be modified, for example blood cholesterol levels in the W.H.O. trial of clofibrate or blood pressure in the trials of anti-hypertensive agents. Thus, in theory at least, the existence of several different pathogenetic mechanisms does not present as great a problem as for secondary prevention trials. But the opportunity of focusing on one mechanism depends on having a valid and biologically plausible measure of risk, such as the blood cholesterol level, which has been shown to be associated with the later occurrence of the disease. There is no such measure of platelet function. The primary prevention trials of aspirin in progress or being planned make use of participants in whom no particular attempt has been made to select those

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at high risk or in whom risk is assessed on 'conventional' risk factors such as blood cholesterol or smoking habit, and which may or may not reflect platelet activity. This is unsatisfactory, particularly as, in statistical terms, the incidence of first i.h.d. events in an unselected group is low so that trials require very large numbers of participants. Platelet function depends not only on intrinsic properties of the platelets themselves but on plasma, vessel wall and haemodynamic influences as well. Difficult and time-consuming though it may prove, tests that reflect these features and are predictive of i.h.d. must be a high research priority if basic knowledge on platelets is to bear full fruit in practical terms.

In both primary and secondary prevention trials, sudden death and myocardial infarction can and probably should be regarded as separate endpoints, for reasons discussed earlier. This means that the number of participants required will have to be based on separate mortality and incidence rates rather than on the rate for both combined.

3. Early entry

Many believe that future secondary prevention trials should be based on very early, if not immediate, entry after infarction. In the second South Wales aspirin trial (Elwood & Sweetnam 1979), half the patients were admitted within 7 days. The interval in the Anturane Reinfarction Trial (1980) was 25–35 days. Otherwise, entry into recent trials (i.e. excluding the anti-coagulant trials) has been between about 6 weeks and several years after infarction. The optimum interval may vary for different drugs, but the general principle of entry within days or a few weeks, rather than months or years, is sound. However, early entry trials raise two major problems.

One difficulty is that very early entry may result in the inclusion of patients who do not stand to benefit, either because it is eventually clear that they have not had myocardial infarcts or because their prognosis is hopeless, whatever treatment they receive. This difficulty can be allowed for by delaying entry for 2 or 3 days. By that time, it will be possible to exclude most of those who have not had infarcts and many of those who have had very serious episodes will have died. Any requirement for exercise testing (suggested earlier) will delay entry still further. It is a matter for judgement whether the possible advantages of such a test outweigh the disadvantages of the delay.

The second difficulty is that drugs other than those tested in the trial will almost certainly have to be administered. A particular example is the likely use of β-blocking agents in perhaps a quarter of those recruited to an early entry trial of aspirin or sulphinpyrazone. This difficulty raises pharmacological questions about possible interactions (§4). It also raises the precise objectives of i.h.d. trials, primary as well as secondary. Are these trials intended (*a*) to test the policy of using a particular drug ('pragmatic') or (*b*) to give a precise assessment of the clinical effectiveness of the drug under ideal conditions ('explicative')? An argument for the pragmatic approach is that it reflects the realities of clinical practice, where several drugs may be used simultaneously and there is no certainty that all the patients will actually take a particular drug in accordance with instructions. Another reason for the pragmatic approach arises from the recurring question of whether to include the results from patients who deviate from the treatment schedule or who default from follow-up. These patients have to be excluded from an explicative trial, to ensure that the results are based only on patients known to have adhered to their allocated treatment régime for most if not all of the trial. But the greater the number of

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patients omitted from the analysis, the greater the risk becomes of biases affecting the comparison of outcome in treated and control groups. This problem is avoided by the 'intention to treat' attitude of pragmatic trials. Analysis is based on all the patients entered, according to the régime to which they were originally allocated, whether or not they adhere to this régime and, as far as possible, even if they default from follow-up. Although the pragmatic approach will probably reduce the power of a trial, a result suggesting a beneficial effect also implies a beneficial effect in explicative terms. This is exemplified by the recent Dutch trial of stopping anticoagulants in those aged 60 years or more. The adverse effect of discontinuing anticoagulants on recurrent myocardial infarction was quite clear on a pragmatic as well as an explicative analysis (Sixty Plus Reinfarction Study 1980). The effect on mortality was suggestive though not significant at a conventional level on the pragmatic analysis; it was highly significant on the explicative. Although stopping anticoagulants is not the same as starting the treatment, the Dutch trial is a reminder that the issue of anticoagulants after infarction has never been satisfactorily resolved.

4. Pharmacological considerations

Further attention to a number of pharmacological topics might increase the value of preventive trials in i.h.d.

(*a*) *Mode of action*

A major stimulus to a clinical trial is knowledge of the action of a drug on some process involved in pathogenesis. But trials demonstrate the clinical benefit (or otherwise) of the drug in question: they do not prove that the drug necessarily confers the benefit by the process that formed the basis for its use in the trial. Thus, clofibrate probably lowers the plasma fibrinogen level (Dormandy *et al.* 1974) as well as that of blood cholesterol. Although the original reason for testing sulphinpyrazone (Anturane Reinfarction Trial 1980) was its effects on platelet function, it has been suggested that it acts as an anti-arrhythmic drug or that it modifies myocardial function (Forfar *et al.* 1980). Increasingly precise information on modes of action is clearly required, to take full advantage of the possibility of selecting patients for trials according to the pathogenetic mechanisms predominantly responsible for their disease or predisposition to it.

(*b*) *Dose–response*

Even for hypotensive agents, dose–response data are far from complete. Most clofibrate trials have used doses that resulted in only modest cholesterol-lowering effects. The early and encouraging results of a Swedish trial of clofibrate and nicotinic acid (Rosenhamer & Carlson 1980) may be due to the relatively large fall in cholesterol levels that it has achieved. (For the reasons discussed in §2*b*, the widespread use of clofibrate is now contra-indicated. But the dose–response effects of the clofibrate trials are nevertheless valid illustrations.) One reason for the uncertain benefits of anticoagulants in the early trials may have been the failure to achieve and then maintain optimal levels of anticoagulation. The clear-cut results of the Dutch trial of stopping anticoagulants probably owe much to the particular attention paid to this point.

(*c*) *Interactions*

It has already been pointed out that in early entry secondary prevention trials, participants will often be exposed to non-trial as well as trial drugs, which may interact. Trial drugs (if more

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than one are used in combination) may also interact with one another. The theoretical possibility of harmful interactions has been a reason for deciding not to proceed with trials which on other grounds seem justified. It is therefore important to try to distinguish between interactions that have a high chance of actually occurring and of being clinically harmful and those that are less likely to occur or, if they do, unlikely to be of any consequence. Interactions between drugs and the characteristics of those who take them, such as their sex or age, may be of a greater relevance than interactions between drugs themselves.

(*d*) *Side-effects*

Trials are an excellent source of information about the adverse as well as the beneficial effects of drugs. Yet common adverse effects could be detected in controlled comparisons involving far smaller numbers than those needed to demonstrate benefits in terms of mortality and re-infarction. These smaller comparisons would not, it is true, detect rare but serious harmful effects such as those of clofibrate on mortality from all causes (Committee of Principal Investigators 1980) or those of practolol. But less serious effects such as lethargy or impotence could be detected, with greater confidence than hitherto, before rather than during or after a major clinical trial. Information thus obtained would be useful in making choices between what may be an increasingly large number of possible drugs. It may be that sulphinpyrazone impairs renal function (Wilcox *et al.* 1980), the evidence to this effect having only become available, however, well after the completion of the Anturane Reinfarction Trial (1980).

(*e*) *Compliance*

Side effects at therapeutic levels and other factors will affect compliance with trial régimes. Again, this is a feature that should be established with some certainty before rather than after the main trial.

In summary, the scale, planning and conduct of clinical trials will benefit from the availability, beforehand rather than afterwards, of increasingly precise and comprehensive pharmacological information.

5. Hypertension and arterial disease

The main stimulus to the detection and treatment of hypertension has been the predominance of raised blood pressure as a determinant of cerebrovascular disease (Gordon & Kannel 1972). This association is much more striking than the relation between raised blood pressure and i.h.d., though raised pressure is also associated with an increased risk of i.h.d. (Gordon & Kannel 1972). There were thus expectations that the treatment of high blood pressure might reduce the incidence of i.h.d. as well as of stroke. In contrast to clear reductions in stroke incidence, however, early trials suggested little or no benefit in terms of i.h.d. (Veterans Administration 1967, 1970). These trials have been followed by others concerned with milder degrees of hypertension. Both the American Hypertension Detection and Follow-up Program (1979) and the Australian Therapeutic Trial (1980) showed significant reductions in mortality from all causes, these reductions being mainly accounted for by cardiovascular disease. It is not clear whether the beneficial effect in the trial in the U.S.A. was due specifically to antihypertensive treatment or to the higher level of general medical care received by those in the more actively treated group. Both trials suggested possible benefits for i.h.d. as well as more obvious benefits for stroke. However, neither of these trials included β-blocking agents as a primary

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treatment. Whether these agents are more effective in preventing i.h.d. than those so far studied remains to be seen. Propranolol is one of the primary treatments in the Medical Research Council's mild hypertension trial (Medical Research Council 1977).

6. Other preventive measures

This review is concerned specifically with prevention by drugs. The primary prevention of i.h.d. by modifications of life-style is, however, widely advocated. These modifications form part of trials (see, for example, Rose *et al.* 1980) whose main results are awaited. Giving up cigarette smoking is an effective method of secondary prevention though this view is largely based on the results of non-randomized comparisons. The growing use of coronary artery surgery as a means of managing angina should also be borne in mind (Second Interim Report 1980).

7. Future directions

For the time being, it has to be accepted that the combination of the low signal/noise ratio and the statistically low event rates mean that secondary prevention i.h.d. trials testing active treatments against inactive placebos will often need 2000 participants, or more. If and when interest shifts to secondary trials of a new agent against an older one of established value the numbers needed may be even larger. Primary prevention trials may call for over 10000 participants, particularly if the latter cannot be selected by a test related to the pathogenetic mechanism to be modified. With the uncertain clinical implications of past trials in mind there are signs of resistance to further i.h.d. trials. This might be justified if it appeared that the prevention of i.h.d. would follow some basic advance in pathogenesis or treatment so fundamental that further large-scale trials were unnecessary. This seems improbable. It is hard to envisage any development – even the discovery of thromboxane and prostacyclin – that would overturn the view of i.h.d. as a condition of many disordered processes, making it unnecessary to test new drugs and to identify patients likely to benefit from them. An alternative to further clinical trials is trial by pharmacological theory, exemplified by predictions of drug interactions in early entry trials or trials using more than one drug, and by much of the controversy surrounding the question of aspirin dose. An almost certain consequence of abandoning clinical trials is that the use of drugs for i.h.d. prevention would be determined by the promotional expertise of the pharmaceutical industry. More and more drugs would join the list of those of uncertain benefit: anticoagulants, aspirin, sulphinpyrazone.

To these rather negative reasons for further trials there is the more positive reason referred to earlier. Although they were inconclusive, secondary prevention trials that have been reported (table 1) have nearly all suggested benefits attributable to the drugs in question. The reductions in event rates characteristic of many of the trials – 20% or so – are often described as marginal. But reductions of this magnitude would be of considerable value in a disease as common as i.h.d. Reductions might be much larger than 20% in groups of patients of otherwise poor prognosis taking drugs that modify the particular pathogenetic mechanism(s) responsible for their disease. It has been suggested that one of the reasons for the unconvincing results of the aspirin trials is that doses were too large, thus inhibiting prostacyclin as well as thromboxane production. But it is at least as likely that the results were a reflection of low signal/noise ratios. On these grounds there are good reasons for further trials, as the need and opportunity arise and

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recognizing that these trials will continue to be large, difficult and expensive for the foreseeable future. There are, however, some measures that can be taken to maximize the chances of useful information.

8. Some solutions

Most of the steps to be taken follow from what has already been said. They include the reconfirmation of some aspects of trial design and analysis that have recently been questioned. The suggestions that follow are not intended to be a summary of trial design and analysis but mostly arise from the particular problems of trials of drugs in arterial disease. Some of the suggestions may enable trials to be smaller than hitherto. Some have the opposite effect. But they should all, if practicable, increase the chances of clear results.

(*a*) *Measures for immediate implementation*

(i) *Randomization*

It has recently been suggested that 'historical controls' can be used as a basis for comparison with treated patients (Cranberg 1979). This approach, using as it does some retrospective data, has the superficial appeal of ease and economy. It is liable to be utterly misleading, particularly in just such situations as the secondary prevention of i.h.d. The biases that can arise from not randomizing may result in an apparent but spurious difference in outcome between treated and control groups of the same magnitude as any true difference (Doll & Peto 1980). Is the difference then due to treatment or to bias? Alternatives to randomization or modifications of it have been suggested (Weinstein 1974; Machin 1979; Zelen 1979) but have not been adopted. At present, and probably indefinitely, there is no acceptable substitute for classical random allocation.

(ii) *Adequate numbers*

It is not only pointless but unethical (Altman 1980) to initiate trials with numbers too small for a reasonable chance of clear results. Failure to demonstrate a drug's benefit in too small a trial does not provide any useful evidence that it is without effect, either. Trials of this sort merely add to existing uncertainty. The economy of numbers suggested by combining sudden death and infarction as outcomes cannot be made if they are considered separately. Another factor tending to increase required numbers is growing concern at the effects of multiple statistical inspections of trial data, as they accumulate. On the other hand, increasing awareness by statisticians of the requirements of clinicians and vice versa is gradually leading to an improved mutual understanding of what can sometimes be achieved with numbers that are less than ideal.

There is no easy solution to the problem of large sample sizes in arterial disease trials but this is not, in itself, an argument against further trials.

(iii) *Factorial designs*

The use of two drugs, either separately or in combination, may have statistical as well as clinical advantages (Armitage 1980). There will be four groups in a two-drug factorial trial: patients on one drug alone, those on the other alone, those on both and those on neither. It may be possible to assess the independent value of the two drugs in a trial no larger than a trial to assess a single drug. In addition, clinicians need information on the benefits of drugs used in combination. The main disadvantage of factorial trials lies in the possibility of drug inter-

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actions. If these are marked, that is if the two drugs used together have markedly greater or smaller effects than the sum of their separate effects, the effect of either drug on its own can only be assessed on half the data, with a consequent reduction in the power of the trial. This highlights the need for as much information as possible, before rather than during or after the trial, on interactions of clinical significance. The use of factorial designs deserves wider consideration than it has so far received. The Canadian trial of aspirin and sulphinpyrazone in cerebrovascular disease suggested a benefit attributable to aspirin, but not to sulphinpyrazone or to both drugs together (Canadian Co-operative Study Group 1978). The benefit was confined to men.

(iv) *Pragmatic analyses*

The reasons for these have already been discussed.

(v) *Distinction between different endpoints*

The reasons for distinguishing between sudden death and infarction have been discussed.

(vi) *Record of all patients*

Records should be kept of all the patients considered for a trial, even if they are not included in it. This simple procedure, rarely carried out, enables some assessment of the extent to which trial patients are or are not representative of all patients with the diagnosis in question. The Anturane Re-infarction Trial (1978, 1980) extrapolated its findings to myocardial infarction patients as a whole, but because of the very high proportion of patients excluded from the trial it is doubtful whether this was justified.

(*b*) *Possible measures for the medium term*

Some measures might have an effect on trials in the medium term, depending on the initiation and outcome of future research.

(i) *Selection by prognosis*

Attention has already been drawn to the considerable advantages of secondary prevention trials that exclude patients likely to do very well or very badly whatever treatment they are given.

(ii) *Pharmacological precision*

It is clear that some important pharmacological questions only arise as a result of large-scale trials. Others arise quite independently while trials are in progress: the implications of prostacyclin, for example. These questions cannot be foreseen. However, some of the features discussed earlier can to some extent be anticipated. If so, the increasingly precise and comprehensive information that may emerge before rather than after future trials can only be of value.

(*c*) *A possible measure for the longer term*

A measure which might, in the longer term, improve trial design and conduct is selection by pathogenesis.

It is hard to imagine much progress towards the selection of patients for secondary prevention trials according to the processes mainly responsible for their first event. Selection by prognosis (§*b*(i) above) may eventually be possible. Participants in primary prevention trials can (and

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have) been selected according to their blood pressure and blood lipid levels. It may eventually be possible to select according to clotting factor levels (Meade *et al.* 1980). A major deficiency, however, is any test of platelet function, as defined in §2*d*, that is predictive of subsequent i.h.d. If and when such a test becomes available, the rationale and conduct of trials of agents that modify platelet function are likely to be improved.

9. Conclusion

Implementing some of these suggestions implies the need for priorities in the field of research on arterial disease and some coordination of ensuing research programmes. This is a controversial topic. There must, though, be some reasonable compromise between the extremes of having no guidelines other than the personal interests of workers in the field and of attempting to override these interests altogether.

The simultaneous frustrations and the potential of trials of drugs in arterial disease are considerable. In a paraphrase of Churchill's description of democracy as a form of government, these trials seem to be the worst way of going about the problem – except for all the other ways that have been tried from time to time.

Note added in proof (23 *April* 1981). Particularly encouraging results have recently been reported from the Norwegian secondary prevention trial of the β-blocking agent timolol. (Norwegian Multicentre Study Group 1981 Timolol-induced reduction in mortality and reinfarction in patients surviving acute myocardial infarction. *New Engl. J. Med.* **304**, 801–807.)

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Discussion

J. McMichael, F.R.S. (2 *North Square*, *London*, *NW*11 7*AA*, *U.K.*). The best-matched secondary trial of polyunsaturated fats was under the M.R.C. (*Lancet* ii, 693 (1968)). It produced no benefit. Massive inter-centre trials are often vitiated by diagnostic differences and interpretations. France has notoriously been under-recording coronary deaths since the war. Experimental viral infections (*Lancet* ii, 821 (1978)) can produce the disease and so, possibly, can other infections. We cannot take rational steps towards prevention until we know more about causes from direct observation and experiment.

T. W. Meade. Clinical trials can provide information on causes and mechanisms as well as on prevention.

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