between previous termination of pregnancy and ectopic gestations. Perhaps the best that can be said for the moment is that the clinical adage, "The best way to diagnose an ectopic pregnancy is to think of it," should now have the rider, "Whether or not the woman has an IUCD in situ."

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Regular Review

Secondary prevention of myocardial infarction—the present state of the ART

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Until we can abolish myocardial infarction by effective primary prevention doctors will still be faced with the task of trying to reduce mortality and morbidity in patients who have recovered from a heart attack. During 1980 the results of several major secondary prevention trials will be published; in the light of their conclusions and of the recent final report¹ of the Anturane Reinfarction Trial (ART) clinicians will need to decide whether the findings should influence their routine clinical practice.

Those who do not remember history are forced to relive it, and the Anturane trial and the forthcoming results from the studies of aspirin and dipyridamole need to be assessed against a backcloth of the past. In the 1950s we had a simplistic concept of myocardial infarction and therefore an equally simplistic view of how its recurrence might be prevented. We believed that myocardial infarction was due to coronary artery thrombosis, that death after infarction was due to reinfarction, and that the prevention of further coronary thrombosis would therefore improve survival. Because thrombosis was seen merely as intravascular clotting anticoagulants were expected to prevent it and thereby reduce mortality. Many trials were mounted to test this series of hypotheses, but no clear and convincing answer emerged.² Nevertheless, the lessons learned from them led directly to the Anturane trial and to the other current studies, while the unsolved problems they posed still need to be remembered.

The 1950s model was too simple. Death after myocardial infarction may be due to the consequences of the infarct itself (pump failure and dysrhythmia) as well as to reinfarction, so that deaths caused by thrombosis and further infarction are diluted by deaths which could not be reduced by an anti-thrombotic regimen. We now recognise that an arterial thrombus is not just a fibrin meshwork: blood platelets and leucocytes are present in large numbers³; and as the coumarin anticoagulants do not modify the behaviour of these cells their presence may provide an explanation for the apparent failure of anticoagulants to prevent reinfarction. Finally, we have now

recognised that sudden death is not synonymous with myocardial infarction and that it is not due to major coronary artery thrombosis, since it occurs in patients with very severe coronary atheroma but no recent thrombus.⁴ The final event is an electrical one, but whether it can be triggered by microemboli formed on severely diseased vessel walls remains uncertain.

Thus the 1960s was an age of disillusionment with the use of anticoagulants for secondary prevention in myocardial infarction, but it taught us three lessons important for our appraisal of the 1980s trials. Firstly, deaths after myocardial infarction are a mixture of the thrombotic (reinfarction), the non-thrombotic group (pump failure and secondary dysrhythmias), and the mysterious (sudden death). Secondly, the presence of fibrin in thrombi did not automatically mean that anticoagulants would be antithrombotic; so, too, the presence of platelets in thrombi does not of itself prove that platelet-modifying agents will be antithrombotic. Finally, part of the disillusionment with anticoagulation may have been our false expectation that just around the corner would be a less-demanding regimen which would dramatically reduce mortality. Clinicians looked at the marginal benefits claimed for anticoagulation and decided that even if the claims were valid the apparent benefit was too small to justify the hassle of conventional anticoagulant regimens. Now, nearly 20 years later, we are still debating the results of new trials in which any apparent benefit is equally marginal.

The recognition that platelets could be having a key role in arterial thrombus formation and that simple substances, unrelated to the clotting cascade, such as adenosine diphosphate,⁵ adrenaline, and noradrenaline,⁶ produced platelet aggregation, led to the search for agents which would modify this new aspect of platelet behaviour. In the test-tube and in animal studies adenosine proved to be an active inhibitor, but its effect was very short-lived.⁷ A vasodilator, dipyridamole, was known to inhibit adenosine deamination, so it seemed logical to test whether it could prolong the platelet-modifying effect of adenosine. Dipyridamole was found, however, to be anti-

thrombotic in its own right in studies on animals⁸ and to modify platelet behaviour in man both in vitro and in vivo.⁹ In the same year sulphinpyrazone (Anturane), which had been developed as a uricosuric agent, was found to prolong platelet survival in man.¹⁰ Its precise mode of action remains obscure, since its action on platelets in vitro is less striking than its effects in an intact animal or in man.

The third contender in the first heat of the antithrombotic stakes is aspirin, which profoundly changes platelet behaviour¹¹ because it irreversibly acetylates the platelet enzyme cyclo-oxygenase, thereby preventing the formation of the powerfully proaggregatory material thromboxane A₂. Aspirin, however, also reversibly inhibits the same enzyme in the vessel wall, thereby stopping the production of the equally powerful antiaggregatory material prostacyclin.¹² Thus, if aspirin fails in antithrombotic trials, the explanation may be either that our theory was wrong and thromboxanes and prostacyclin have no direct relevance to spontaneous human thrombosis or that the theory was correct but the wrong dose of aspirin was given. Conventional doses of aspirin of 1200 mg or so daily might prove ineffective in thrombotic disease because they are blocking the generation of both the "bad" thromboxane A₂ and the "good" prostacyclin. Lower doses given intermittently might keep platelet cyclo-oxygenase suppressed while allowing the reversibly inhibited cyclo-oxygenase in the vessel walls to recover. A theoretically appropriate antithrombotic aspirin regimen might perhaps be 300 mg or less every third day rather than 300 mg four times every day—a thought that must be unwelcome for groups just completing major studies based on aspirin in conventional doses.

All three agents being tested in current major clinical trials were therefore developed for other purposes (dipyridamole as a vasodilator, sulphinpyrazone as an agent for treating gout, and aspirin as an analgesic and antipyretic). All had been in widespread clinical use for these other purposes and had proved safe, so that they could move straight into clinical trials in vascular disease. Newer drugs being developed to take advantage of our better understanding of the behaviour of platelets (thromboxane synthetase inhibitors and prostacyclin analogues) will have to undergo a long process of development and testing before a start can be made on the very large trials needed to assess their contribution to the secondary prevention of myocardial infarction.

Results so far—How, then, have the three drugs currently available fared in the secondary prevention race? Dipyridamole alone has not been shown to influence outcome, but the results of a very large-scale trial of dipyridamole in combination with aspirin is to be reported during 1980. The protocol for this Persantin-Aspirin Reinfarction Study (PARIS) allows patients to be admitted for up to five years after their initial infarction; by this time the risk of death from other diseases which cannot be modified by antithrombotic agents must begin to overshadow the risk of death from reinfarction, making success or failure more difficult to judge.

Aspirin has been the subject of several large postinfarction studies in Europe and the United States. In Cardiff, an early study using a low-dose aspirin regimen (300 mg daily) hinted at benefit, but when it was extended to include other centres with modified entry criteria the apparent benefit disappeared.¹³ The Cardiff group has now made a valuable contribution by carrying out another study using 900 mg daily but has failed again to show a benefit on total mortality.¹⁴ A major United States trial (the Aspirin Myocardial Infarction Study or AMIS) has also recently reported that one gram of aspirin

daily does not reduce mortality after myocardial infarction.¹⁵ There is therefore no acceptable evidence from clinical trials that aspirin in conventional or lower dosage can reduce mortality after myocardial infarction. If, as seems possible, we are still left in doubt about the value of aspirin when the other current trials have reported, we need to look back to the anticoagulant era and ask whether it is our theory which has let us down: aspirin may modify some aspects of platelet behaviour, but have these activities any physiological or pathological importance? Alternatively, might the design of the clinical trials have been at fault? Studies both of stroke and of venous thromboembolism have shown sex differences in the effectiveness of aspirin, men deriving benefit but not women.^{16 17} Detailed analysis of AMIS and PARIS may help to resolve whether there are other hidden subgroups in survivors of myocardial infarction.

The trial which has aroused most interest and controversy has been the Anturane Reinfarction Trial (ART).¹ The theory which lay behind the trial was that since sulphinpyrazone modified the survival of platelets it might also have antithrombotic activity, and a reduction in reinfarction rate was the marker chosen as the end point. We have already seen that sudden death is not necessarily a thrombotic end point, and yet it was a modification of this unlooked-for event which emerged from the trial. Reinfarction risk had been assumed to persist throughout the years after the initial infarction (if it did not, the late-entry facility in AMIS and PARIS would be meaningless), whereas the haemodynamic and arrhythmic consequences of an infarct become less and less important with time in a group of survivors. An effective antithrombotic regimen would therefore have been expected to produce a steady divergence of the survival curves once the initial post-infarction period had passed, whereas an effective anti-dysrhythmic regimen would be expected to push the curves apart in the immediate postinfarction period—but thereafter the lines would run parallel.

The second unexpected finding to emerge from ART was that survival showed the second pattern (early divergence and subsequent parity) rather than the first (early parity and subsequent divergence). Entry to ART was from the 25th to the 35th day after infarction, so raising a crucial question: would the lines have diverged even more sharply had the trial been started as soon as possible after infarction? Might the sulphinpyrazone be exerting an antiarrhythmic effect, either directly on the myocardium or through a modification of platelet behaviour? Unhappily, only a new early-entry study can answer this major question. Might sulphinpyrazone be working in some other way? If we accept that it reduces mortality after infarction, does it operate via the link between uric acid and death from coronary heart disease?¹⁸ Might sulphinpyrazone be altering outcome through the property for which it was developed (its uricosuric activity) rather than through its effect on platelet survival? Thus, like any good scientific experiment, ART has posed more questions than it has answered, but the unexpected results (a reduction in sudden death rather than in reinfarction and an early, time-limited effect rather than a continuing one) require us to look very carefully at the strengths and weakness of the design and analysis of the trial.

Firstly, entry to the trial must have been highly selective, in that the major centres which were used recruited only an average of three patients a month. This high degree of selectivity does not invalidate the results of the trial, but without more explanation of why some patients were included while most were not we must be cautious about extrapolating from

the results by suggesting that all patients with myocardial infarction would be helped by sulphinyprazole.¹⁹ Secondly, in the conduct of the trial, theoretical consideration was given to the time after entry at which the drug might be assumed to have become effective. On the basis of studies of foreign surface dialysis shunts this was thought to be seven days so a seven-day rule was applied and deaths were divided into "analysable" and "non-analysable." In studies such as this, where a pragmatic end point is sought to guide the practising doctor, the only acceptable analysis of outcome is one based on intention to treat; if we look at all deaths in all "eligible" patients (whether "analysable" or "non-analysable") the difference in total outcome between the placebo and the sulphinyprazole groups moves right to the edge of conventional significance.

Furthermore, the reader cannot carry out a complete, all-comers, "intention-to-treat" analysis for himself because he is not given the necessary information. In the earlier interim report,²⁰ 101 of the 162 patients who had then entered the trial had been excluded after entry, but this group cannot be identified in the final report. In the latter, we also find that there were 71 entered patients who were later found to be "ineligible" so were excluded from analysis. The outcome in these two groups should have been made clear so that an analysis could be performed on the basis of total outcome. We should also note that the trial had a very high dropout rate (415 withdrawals from 1629 entrants), which not only gives rise to problems of analysis but reminds us that we should be cautious in extrapolating from the trial results to a total population of survivors of myocardial infarction.

Two other features trouble me. In the earlier, and in my view premature, interim analysis which was published and widely publicised,²⁰ a high ratio of inferior to anterior infarcts occasioned surprise. In the final report this ratio has changed considerably. No doubt local interpretations of the strength of the electrocardiographic evidence of infarction may differ from those of a central review group, but I am puzzled to find that the siting of infarction and the identification of bundle block should have given rise to such considerable difficulties. I also note that of the 106 analysable deaths occurring during the trial period all except one were attributed to cardiovascular causes. In our own more limited trials on beta-blockers and home versus hospital care at Nottingham we have found that ordinary diseases are not prevented by

participation in a clinical trial. We have met lung cancer and other common neoplasms, bronchopneumonia, renal failure, stroke, pancreatitis, road traffic accidents, and the like. Were all the deaths in ART except one really cardiovascular?

Among the major questions that remain unresolved after ART are: how does a uricosuric, platelet-modifying agent prevent sudden death? Would this effect be even more valuable in a very-early-entry study? Does the highly selected trial population with its complex categories of eligibility and analysability tell us how sulphinyprazole would fare in clinical practice? Should we immediately bring it into widespread general use, as has been strongly advocated,¹⁹ when the case for this blanket recommendation rests on a differential of 15 sudden deaths between the two ART groups? Alternatively, would practising clinicians consider that the reduced significance of the difference in total mortality which emerges from an intention-to-treat analysis of all eligible patients should prompt us to be cautious, since this evidence falls short of proof?

These unresolved questions have been reiterated to remind us why history must be remembered if it is not to be relived. Confusion and weariness ended the anticoagulant era: we were left with no results on which we could base our practice. This must not be allowed to happen with the three first-heat runners in the new antithrombotic stakes. We must remember that we are testing our hypotheses about causation as well as testing the efficacy of treatment. We must ensure that trials of dipyridamole, aspirin, and sulphinyprazole, both current and planned, are brought to a firm conclusion, and we must insist that the results are presented with every scrap of evidence. The experience thereby gained should enable us to handle the runners in the next heat (thromboxane A₂ synthetase inhibitors, and prostacyclin analogues) more swiftly and confidently, and ensure that these trials will increase our ability to give practical advice to clinicians managing patients who have survived their initial myocardial infarction. For the present, my verdict on the claim that the report of the ART has altered the state of the art must be one of "not proven."

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