Regular Review

"But will it help *my* patients with myocardial infarction?" The implications of recent trials for everyday country folk

J R A MITCHELL

"As a grown man you should know better than to go around advising people."—Bertolt Brecht in *Mother Courage*.

"I hope for his own sake that he has younger people than me at his disposal if he wishes to ask for bad advice; especially if he means to follow it."—Marcel Proust in *Cities of the Plain*.

The myocardial infarction battlefield is littered with bad advice, and yet each discarded dogma was initially hailed as "the answer" to the management of this common and lethal condition. At first the idea of promoting healing of the damaged myocardium by prolonged bed rest dominated the scene. White¹ claimed that "rest in bed for weeks or months should be prescribed in order to ensure as sound a healing of the myocardial infarct as possible, with very gradual or careful convalescence." Lewis,² clinical scientist though he was, was not immune to clinical belief unbacked by evidence when he said that "rest in bed should be continued for from six to eight weeks to ensure firm cicatrization of the ventricular wall: during the whole of this period the patient is to be guarded by day and night nursing and helped in every way to avoid voluntary movement or effort. Patients have lost their lives . . . by neglect of these precautions." When Sam Levine dared to challenge this in 1944 with his "armchair" regimen he was vilified as an unethical heretic, but as soon as actual trials were done they showed^{3,4} that the period of bed rest could be progressively reduced without influencing mortality at all, and indeed, in some studies,⁵ with less residual disability. But even as one dogma was being thrown aside new ones were being forged for use.

Oxygen administration was claimed⁶ to be beneficial in acute infarction, and "even in patients with good circulatory function the theoretical advantage of improving oxygenation of the myocardial tissue involved by infarction is a powerful argument which in the present state of knowledge is open to little criticism. From a practical standpoint the routine administration of oxygen to all patients with myocardial infarction is indicated." Barely was the ink dry on this pronouncement than the obsession with myocardial healing and salvage began to wane and give way to the equally single-minded pursuit of arrhythmias. Clinicians were told⁷ that "sudden death in patients with myocardial infarction is not the inexorable consequence of extensive myocardial damage, but rather the result of a reversible derangement in heart rhythm. Minor irregularities of the heart beat precede ventricular fibrillation or cardiac asystole. These findings have changed the focus of care from resuscitation to that of abolishing minor arrhythmias. Prompt control of arrhythmias reduces mortality of the

hospital patient by 30%." Large numbers of patients must have been harmed in the pursuit of this dogma by the routine administration of lignocaine or atropine before the data from proper clinical trials had become available.⁸ Now, more cautious counsels⁹ can be offered: "It is possible that the benefits of lignocaine were restricted to patients without congestive heart failure, to the younger patients, to those enrolled early, or some combination of all three. Until subsets of older patients or those with complicated myocardial infarction can be studied separately, the benefits of lignocaine prophylaxis in such patients should probably be considered unproven."

The search for the "warning arrhythmias," which were the holy grail of the 1970s, made it necessary to admit patients to coronary care units and to treat the oscilloscope rather than the patients. Most district general hospitals set up such units but as Rose pointed out,¹⁰ they "are expensive consumers of scarce resources and it is unfortunate that there has been little attempt to evaluate their achievements." At that time the Bristol and South-west study had already shown that for patients with uncomplicated infarcts who were first seen some time after onset there was no advantage in terms of mortality even in admission to hospital, never mind to a coronary care unit. Since then our own study¹¹ has reinforced this finding, so that if Rose¹⁰ were reconsidering his advice today, I suspect he could still say "Should hospitals without coronary care units hurry up and get them? . . . there is little positive evidence that they should. Should general practitioners send all their patients with acute myocardial ischaemia to hospital? There is no simple answer and . . . for the good risk case the only available hard evidence is in favour of staying at home."

Lessons for today

If the entrenched dogmas of the past (bed rest, oxygen, coronary care units, and prophylactic antiarrhythmics) are now being discarded or being applied more selectively, then what is taking their place—since medicine abhors a vacuum and physicians do not like to admit that they have little to contribute, especially when their advice and treatment is being offered in the market-place? Wenger and her colleagues¹² have documented the exchange of the old for the new between 1970 and 1980 in the United States and have shown that "the median length of hospitalisation has decreased markedly. Early ambulation and an earlier return to work are more common but 'the prescription of prophylactic antiarrhythmic agents has increased . . . the use of standard exercise tests has

increased," and there is now "the routine use of coronary angiography by a large percentage of physicians." Doctors caring for patients admitted to hospital with myocardial infarction are only too well aware of the flood of publications urging them to adopt new diagnostic procedures (isotope imaging, exercise testing, and coronary arteriography), to use more aggressive acute treatment (streptokinase, nitroprusside, hyaluronidase, and beta-blockers) and to use beta-blockers as a postinfarction routine. How much of this advice will follow its predecessors on to the scrap heap? In my scrutiny of the tidal wave of papers I have tried to decide whether they represent wisdom, knowledge, or merely information, and have tried to assign them to four categories. These are:

Firstly, a case has not yet been proved. We can all relax for a year or two while better trials are being done or, if we are energetic, we can do them ourselves.

Secondly, though a case appears to be proved, the trials have been done on a subset of patients who either do not correspond to or form only a small part of the patients with acute myocardial infarction presenting to the average district general hospital.

Thirdly, a case is proved but the techniques required are not available where the patients present. We must then campaign for the facilities to be made available locally or refer our patients to centres where they already exist.

Finally, a case is proved for something which we can all do immediately, so we should get on with it.

On arrival

My starting point is the patient with suspected infarction admitted to the coronary care unit or medical ward of a district general hospital. This inevitably excludes the crucial problem of prehospital deaths, which account for about half the mortality from onset to one year and which requires community action from doctors, nurses, ambulance men, trained lay people, and the mass of the general public. The first challenge facing the ward team is to decide whether the patient they are seeing, who has usually presented with chest pain (though patients with "collapse," heart failure, or arrhythmias will also enter the diagnostic stakes), has actually got a myocardial infarct. It would be pointless or possibly harmful to apply complex manoeuvres which had been validated only on patients who had undergone multi-lead electrocardiography, complex cardiac enzyme measurements, isotope scanning, and possibly coronary angiography to a patient who had just arrived in our own wards. There, all we have to guide us initially is the history and the first 12-lead electrocardiogram, since the cardiac enzyme values will be neither available nor diagnostic. At this stage the term "suspected infarction" is simple and honest, and to cloud the issue by terms which imply that we know what is about to happen such as "impending infarction," "unstable angina," and "preinfarction syndrome" only serves to create confusion when trial results are presented.¹³

Confronted with a patient with suspected infarction, our initial task is simple: to place the patient so that if he tries to die from ventricular fibrillation he will be noticed by skilled nursing staff and kept alive. Concentrating such patients in special units makes organisational sense provided that the staff do not become obsessed by technology at the expense of common sense. The function of a circulation is to perfuse, so if the top end of a patient is reading its newspaper and conversing, if the middle is eating its dinner, and if the lower part is

producing urine then the oscilloscope need not be studied, still less used to determine "treatment." If beds in a coronary care unit are not available, beds in a general ward near the nursing station may be equally acceptable if the hospital rotates all its nursing and junior medical staff through its coronary care unit so that there is a high general level of awareness and skill. What makes no sense is to place a patient with a suspected infarct in a remote corner of a general ward and hook him up to a bedside monitor which is either ignored by everyone or which produces panic from time to time because muscular movements are misinterpreted as cardiac arrhythmias.

Early stages

In the early stages of infarction, therefore, the diagnosis is immaterial since management is not influenced. Nevertheless, can we get any clue in the pre-enzyme period to the likely eventual diagnosis? We have found an association between the amount of analgesia used on an "as-required" basis and the strength of the final diagnosis. This idea that the severity and duration of chest pain in the first 24 hours correlate with the size of the infarct is supported by Ledwich and Mondragon,¹⁴ who found that patients whose chest pain lasted longer than eight hours had greater enzyme activities, more ST shift, and more Q waves than patients with shorter periods of chest pain. In the admission procedure for suspected infarction, then, all we need to do is site the patient where he can be resuscitated if he develops ventricular fibrillation, be generous about pain relief (which doctors and nurses are usually not), and to consider whether the number and frequency of doses of diamorphine can actually be used to make the diagnosis.

Once we have made the patient safe and comfortable does diagnosis matter in the next few days? It clearly does if we are proposing to use techniques to limit infarct size or lyse coronary thrombi. Also, at a very pragmatic level, beds in coronary care units, monitors, and skilled nurses are often at a premium, so an early diagnostic classification which correlated closely with risk and with outcome would be useful in deploying scarce resources to best advantage. There is abundant evidence that as the serial changes in the electrocardiograms unfold and the cardiac enzyme results become available such stratification for risk is possible. Mulley and his colleagues¹⁵ showed that of 360 patients admitted to their unit the 168 who had no rise in enzyme activities, no complications, and no electrocardiographic evidence of transmural infarction by 24 hours could be confidently labelled as "low risk," since none of them died during their hospital stay, whereas their intermediate and high-risk groups had 4% and 9% hospital mortality rates.

Not everyone agrees that risk can be calculated so neatly,¹⁶ but our own experience may provide the clue to this disagreement. We found¹⁷ that when we categorised patients with first infarcts according to defined criteria¹³ into definite, probable, and possible myocardial infarction; other definite diagnoses; and a residual group of "chest pain ?cause" then the last group, who accounted for 13% of the 662 patients studied, had a zero mortality in the subsequent 12 months. In contrast, patients who had had a previous myocardial infarction and whose index admission rated only "chest pain ?cause," in that there were no diagnostic electrocardiographic or enzyme changes, had a mortality of 7% at one year. We concluded that, while it is easy to rule out infarction in patients with a first episode, great caution should be exercised in ruling out

infarction in patients with previous episodes, since the scarred heart may find it more difficult to declare the presence of a new lesion in respect of electrocardiographic and enzyme changes.

Attacking the infarct

BETA-BLOCKERS

What I have described so far is an essentially passive approach which poses no problems for any hospital and which contrasts sharply with the frenetic "warning arrhythmia" activity of the past decade. But surely we should be doing something about the infarct itself and the subtending thrombus that produces it, as opposed to the passive policy of pain relief and resuscitation from ventricular fibrillation? As soon as beta-blockade became a practical proposition the antiarrhythmic effect of the drugs was thought likely to reduce mortality in acute myocardial infarction. In contrast with the evidence in favour of the use of beta-blockers in the post-infarction period, which we shall meet later, the results of studies in acute infarction were confusing and disappointing. It has, however, been argued that the "too little, too late" philosophy, which was built into the trial protocols, was responsible for the failure to detect an early beneficial effect in human infarction to match the effect seen in animals.

Norris and his colleagues¹⁸ gave propranolol 0.1 mg/kg intravenously to 20 patients within four hours of the onset of suspected infarction and found that, in comparison with an imperfectly matched control group of 23 patients, the serial electrocardiographic and enzyme changes were less pronounced. As Sobel¹⁹ commented, "The absence of long-term follow-up data clouds the overall effect of the treatment regimen." In other words, what matters to patients is survival; electrocardiograms and enzyme values butter no parsnips with them since it might be possible to limit the manifestations of infarction by agents which depressed enzyme release or suppressed electrocardiographic changes without altering the infarct itself.

If that is all that beta-blockers do then an even cheaper way to limit enzyme and electrocardiographic changes is to refrain from measuring them. There may be more to the story than that cynical view, however—for example, in a tightly executed study of metoprolol, Hjalmarson and colleagues²⁰ began with an intravenous injection of 15 mg given as soon as possible after admission and followed by 100 mg twice daily by mouth. The interval between onset of symptoms and the intravenous injection was some 11 hours, and many would argue that irreversible changes in the heart muscle develop within minutes rather than hours.²¹ In addition to an overall (intention-to-treat) reduction in 90-day mortality, they observed that "metoprolol caused a 15% reduction in enzyme-estimated infarct size among patients treated within 12 hours after onset of pain . . . only 32 patients in the metoprolol group compared with 55 in the placebo group were given lignocaine for the treatment of ventricular tachycardia and fibrillation. It therefore seems reasonable to believe that metoprolol has beneficial effects during the first days of acute myocardial infarction."

The answer to this question will undoubtedly come from an extension of the early intravenous atenolol study carried out by the Oxford group,²² which showed a reduction in infarct size as determined by enzyme activities and the electrocardiogram, the median time from onset of pain to injection being four hours. Sleight and Peto are now mounting a simple trial throughout Europe to assess the effect of early beta-blockade

on mortality, and until they report we can either sit back or offer to join them and speed the trial on its way.

One would have thought that the lessons of the past would have made editors sceptical of anything with inadequate numbers, imprecise entry criteria, and end points which might be statistically significant but which defy common sense. Not so, for we are urged²³ to use a combination of heparin and atenolol in the "intermediate coronary syndrome," whatever that is, because two deaths occurred in the double-placebo group during the first seven days of the trial and three in the placebo-heparin/atenolol group over the next seven weeks in comparison with no deaths in the heparin alone or heparin-atenolol group. There are times when a reviewer feels weary because we seem to have forgotten nothing but learnt nothing.

HYALURONIDASE

The initial hope for beta-blockers lay in their antiarrhythmic effect, and only now is an infarct-limiting strategy being explored. Other agents entered this race over a decade earlier. On the basis of animal studies, hyaluronidase was thought likely to improve the diffusion of nutrients into ischaemic tissue by altering the mucopolysaccharide composition of membranes and support tissues. Maroko and colleagues²⁴ found that given intravenously after the first diagnostic electrocardiogram and thereafter six-hourly, hyaluronidase "reduced the frequency of electrocardiographic signs of myocardial necrosis." Given the date of the paper it is astonishing that no reference is made to cardiac enzyme values, but in the light of the recent paper by Flint and colleagues²⁵ this may not have been a simple oversight. The Birmingham group gave a single intravenous injection of purified hyaluronidase or placebo to patients presenting within hours of onset and found that the six-month mortality was reduced (27 of 240 patients given enzyme and 45 of 243 patients given placebo died). Despite this favourable trend in mortality the treated patients showed no reduction in infarct size as judged by enzyme activities or the incidence of heart failure. Oliver²⁶ has drawn attention to a curious feature of the study in that the benefit was almost entirely confined to patients with heart failure. The authors themselves remained uncertain about the mechanism of action of the agent and thought that much larger trials would now be justified to confirm their findings.

In a smaller trial,²⁷ however, the results of Cairns and colleagues reinforced the lack of effect of hyaluronidase on infarct size: 26 patients given the agent six-hourly for 42 hours did not differ in respect of enzyme values from 22 given placebo. Over 10 hours had elapsed from onset to injection in a quarter of their patients, and when patients treated within six hours were analysed the reduction in infarct size was greater, albeit still not significant.

Attacking the thrombi

But why concentrate on the horse instead of repairing the stable lock, and why do we not attack the subtending thrombus? In the 1960s, early trials of systemic fibrinolytic treatment yielded beneficial results, but as in many topics, the next generation of more tightly controlled studies failed to confirm or refute benefit from streptokinase or urokinase.²⁸ A European co-operative study group²⁹ made what will almost certainly be the last contribution to the study of systemic lytic treatment by

a trial in 315 patients treated within 12 hours of onset. All the patients received anticoagulants, but the active-treatment group also received intravenous streptokinase for 24 hours. By the sixth month 48 control patients and only 24 given streptokinase had died. A curious feature was that, although the treatment was given for only a day, late deaths were more appreciably reduced than early deaths (by 21 days, 28 control and 18 treated patients had died, but between 21 days and six months, 20 further patients in the control group perished but only six of those who received streptokinase). What we must note, however, is that, of 2338 patients considered for entry to the trial, only 315 (13.5%) were entered. Readers must judge for themselves whether systemic lytic treatment comes into my first, unproved category or my second category of proved but of doubtful applicability.

Logistic problems

As all patients suspected of having an infarct probably have a venous line introduced to give ready access to the circulation in emergencies, what I have been describing so far would pose no problems for any of us. If early intravenous beta-blockade, hyaluronidase, or streptokinase is found to be of value and to do no harm, then the logistic problems in adopting it as routine treatment are minimal in terms of equipment, manpower, and finance. Not so with the 1980s excursion into thrombolytic treatment, which is to infuse streptokinase into the occluded arteries, thus requiring the full panoply of coronary angiographic facilities. Given between 2.3 and 4.3 hours after the onset of symptoms³⁰ to nine patients with coronary occlusions, patency was restored within 20 minutes but in one patient the artery became reoccluded. Myocardial perfusion was assessed with radioactive thallium and was found to be improved after thrombolysis, but the authors wisely concluded that "evaluation of the long-term effects of this procedure on survival and myocardial function will require controlled clinical trials." That the streptokinase was having a direct effect as opposed to the more occult long-term beneficial effect seen in the European systemic study was confirmed by Reduto and colleagues,³¹ who showed that they could clear the obstruction and improve left ventricular ejection fraction in 18 of 26 patients with total occlusion, whereas patients with severe stenosis were not benefited.

In my view, acute intracoronary thrombolysis has about as much relevance to the community problem of coronary disease as does a flag-carrying national airline or a Western-style medical school to a developing country. The mind boggles at the thought of carrying out coronary arteriography in all patients with suspected infarction who are seen within four hours of onset, and the impact of such a development on demands for finance, medical and nurse staffing, and equipment would be enormous. Moreover, coronary arteriography may kill and is not for the amateur; "myocardial salvage units" would initially need to be based in existing subregional invasive cardiology centres, so locally we would face the prospect of all the district general hospitals in the Trent region, with its population of five million, sending their patients with early infarcts to the three investigative centres in Sheffield, Leicester, and Nottingham. There has to be another way.

The final acute intervention which we must evaluate is the idea of taking some of the load off the heart with vasodilators. Two conflicting reports appearing on consecutive pages of the same journal show how difficult life can be for the unwary.

In the first study, carried out in Amsterdam,³² intravenous

nitroprusside was given to 163 men and women with myocardial infarcts seen within 24 hours of onset while 165 patients received glucose infusions. The trial was stopped on ethical grounds when deaths among the controls reached 18 in comparison with five in the nitroprusside group. The authors claimed that the infusion also reduced cardiogenic shock, heart failure, and peak enzyme activities but the crucial question they should have asked themselves is, "Were our groups comparable in all respects other than the regimen under scrutiny"? The answer would have been "no," because 23% of the control group were in heart failure on admission as compared with 15% in the nitroprusside group.

The second study was carried out by a Veterans Administration group³³ and was therefore confined to men. It was also restricted to patients who had heart failure as defined by a left ventricular filling pressure of at least 12 mm Hg. Nitroprusside was given for 48 hours to 407 men and placebo to 405, and the mortality rates were 11.5% and 10.4% at 21 days and 17.0% and 19.0% by 13 weeks. The authors also noted that nitroprusside "had a deleterious effect in patients whose infusions were started within hours of onset"—13-week mortality for nitroprusside 24.2% and for placebo 12.7%—but "a beneficial effect in those whose infusions were begun later"—13-week mortality for nitroprusside 14.4% and for placebo 22.3%. As Lewis Carroll³⁴ said, "He thought he saw an argument that proved he was the Pope. He looked again and saw it was a bar of mottled soap. A fact so dread, he faintly said, extinguishes all hope."

The differences between the trials are crucial: the larger Veterans Administration study had well-balanced groups but a later entry point and all its patients had heart failure. The European study was smaller, had imbalanced groups, but was earlier in entry and only some of its patients had heart failure. The trials remind us, as did the conflict about sulphapyrazone, of the folly of raising statistics above common sense. Reducing two deaths to one could be claimed as a 50% reduction but would be unlikely to achieve acclaim. The actual European deaths³⁵ were 18 for control and five for nitroprusside, which as "an enormous 72% reduction, is statistically significant and biologically extraordinary. However, mortality was relatively low in both groups and this makes it possible for small changes in the difference between the groups to result in large swings in significance levels. Thus the observed difference of 13 deaths is statistically significant but significance would have been lost if the difference had been nine deaths." In other words, back to the drawing board, and, while we are sharpening our pencils, what about other vasodilators such as captopril, prazosin, and the prostaglandins PGE₁ and PGI₂? While we are testing vasodilators we should also remember that platelets resemble vascular smooth muscle, and it has long been known³⁶ that most vasodilators have effects on platelets which could be favourable in thrombotic disease.

Surgical attack

Before allowing our hypothetical patient with a suspected infarct to continue his convalescence we need to scrutinise the role of surgery in the acute phase. The mesmeric effect of words looms large here, because even the enthusiasts would have recognised that dead heart muscle is unlikely to be helped by aortocoronary bypass grafting. On the other hand, the siren voices that lure enthusiasts on (and sometimes they do not recognise that the voices are their own) argued that if only they could intervene during "impending infarction," "threatened

infarction," "coronary insufficiency," or "unstable angina" then surely they could prevent death of muscle. We have already described¹³ the confusion which has resulted from such imprecise labels,¹⁸ and probably the worst of them all is "unstable angina." Some order now seems to be returning to the scene, however; a valuable early-warning note was sounded by Selden and colleagues,³⁷ who took 40 patients with "acute coronary insufficiency" and randomised them to medical or surgical treatment, the median interval between admission with pain and randomisation being two days. They found that by four months there were no deaths and two completed infarcts in the 19 medical patients compared with one death and three infarcts in the surgical group. By 1980, increasing exception was being taken to "unstable angina"³⁸ and there were by that time enough studies for the analyst to say "the results point to a higher myocardial infarction rate with surgical treatment and no difference in mortality rate. There is no place for immediate surgery."

Reports since then have reinforced this view, in that a national co-operative study,³⁹ which allocated 102 patients to medical and 100 to surgical treatment, showed a mortality rate in hospital for patients with proximal left anterior descending coronary artery disease of 2% after medical and 9% after surgical treatment, the non-fatal infarct rates being 9% and 23% respectively. Finally, at a consensus development conference of the National Institutes of Health, Russell *et al*⁴⁰ advised that "urgent surgery for unstable angina is not necessary to prevent death or myocardial infarction."

Don't forget the veins

While our patient has been progressing from suspected infarction to a definitive diagnosis he has also been at considerable risk from venous thromboembolism in that the results of ¹²⁵I calf scanning become positive in roughly 30% of patients with complicated infarcts, in 20% of those with uncomplicated infarcts, but in 10% or less of those with chest pain ?cause.⁴¹ Whatever their long-term contribution to the prevention of recurrent infarction may be (and we shall scrutinise this presently), when coumarin anticoagulants are used properly in the short term they prevent deep vein thrombosis and pulmonary embolism. Even at 48 hours after infarction, the Danish study⁴² showed a reduction of clinically manifest or proved-by-necropsy venous thromboembolism from 14% in their control group to 10% in their treated group. The Medical Research Council trial,⁴³ which covered the 28 days after infarction but which did not achieve optimal anticoagulant control, found thromboembolic end points in 79 of 715 control patients but in only 34 of 712 treated patients. None of the trials, unhappily, was pushed to the point where an intention-to-treat effect on total mortality was obtained, nor is it clear whether mural thromboembolism from the endocardial surface of infarcts is reduced by coumarin treatment. If, however, your patient is sick or is needing to remain immobile in the coronary care unit because of his rhythms or heart failure then a decision about anticoagulation is required.

"Can you stop it happening again, Doctor?"

During the past decade we have been urged to prescribe materials which modify platelet behaviour in the hope that these changes will prevent further coronary thrombotic

occlusion and reinfarction. The first agent for which a beneficial outcome was claimed was the uricosuric agent sulphinpyrazone (Anturan). There were, unhappily, grave defects in the design, analysis, and reporting of the Anturan Reinfarction Trial,⁴⁴ and when the results were able to be presented on a total mortality and intention-to-treat basis, the highly favourable effect on an ill-defined end point labelled as "sudden death" which had figured prominently in the early publications and the advertising literature was not found to affect total outcome.

A second trial (Anturan Reinfarction Italian Study) comparing the outcome at about 20 months after entry in 365 postinfarction patients receiving sulphinpyrazone and 362 receiving placebo, showed 29 deaths on an intention-to-treat basis with the drug and 27 in the placebo group.⁴⁵ Non-fatal end points were reduced (16 v 37) but if the reason for worrying about acute myocardial infarction is that it kills you then an effective prophylactic should save your life and reflect itself in the mortality figures. The Italian trial was too small to show an effect on overall mortality and so, until better trials are mounted (and I do not believe that they will be), the verdict must be not proven, thus placing sulphinpyrazone in my category 1 (which implies that you can ignore it without feeling guilty or, alternatively, if you do feel guilty you can do a better trial and give us all some extra knowledge).

Also running in the secondary prevention stakes⁴⁴ were dipyridamole (Persantin) and acetylsalicylic acid (aspirin). As an individual runner, dipyridamole never left the starting gate, but it also ran as a partner in a three-legged race with aspirin (Persantin Aspirin Reinfarction Study—PARIS). Aspirin alone was tested in the Aspirin Myocardial Infarction Study and in two studies organised by Elwood and his colleagues from South Wales. In none of the trials has there been a reduction in total mortality on an intention-to-treat basis. It has been argued that it is possible to bring the results of the various trials together and to calculate that there might have been a real, but hidden, beneficial effect of aspirin on mortality of the order of 5-10%. Nevertheless, even when analysed in this way, which we shall meet in respect of the beta-blocker trials, the confidence limits of this possible benefit embrace zero, so the strongest statement which I feel able to make is, "It won't do much harm, but it is unlikely to do much good."

To anyone who is routinely using aspirin alone or in combination with dipyridamole after infarction I would say that I recognise the impotence that you feel at being unable to do anything useful, but this often reflects itself in treatment being given to make the prescriber feel better rather than the patient. To such colleagues I would say that if you want to do something for which good evidence exists, then switch to beta-blockers; if you want to contribute to knowledge, then put your patients in a trial.

The aspirin controversy is not yet over⁴⁶; when many of the trials were conceived it seemed possible that aspirin was going to exert any beneficial effects through its action on the blood-clotting system. In this respect doses of 100 mg and 300 mg daily have no effect, but when doses of 1000 mg or more are given daily there is a reduction in concentrations of factors II, VII, IX, and X, just as with the coumarin anticoagulants.⁴⁷ All the aspirin trials except one used doses of about 1000 mg a day, so if aspirin is really working as an anticoagulant then would doses of 1500 mg a day have produced clearer benefit, albeit at the expense of side effects? While the trials were being planned it became clear that platelet activities were also substantially affected by 1000 mg of aspirin daily, so the trials were conducted in the belief that these platelet properties were

"bad things," that they were contributing to the thrombotic actions of platelets, and that they would be favourably modified by aspirin. But even as the reports were being written it became known that aspirin not only suppressed potential "baddies" in platelets by inhibiting the production, by cyclo-oxygenase, of the proaggregatory vasoconstrictor thromboxane A_2 but it also prevented the same enzyme system in vessel walls from manufacturing the antiaggregatory vasodilator, prostacyclin (PGI_2).

If a balance between this vessel-wall "goody" and a platelet "baddy" is important in the thrombotic process then doses of aspirin which suppressed both might have no useful effect, whereas doses which inhibited platelet thromboxane A_2 while leaving vessel-wall PGI_2 intact would be beneficial. Our own evidence^{48 49} suggests that if such a dose regimen exists, it is of the order of 40 mg (half a Junior tablet) every second or third day. To my "aspirin a day keeps the infarcts away" colleagues I would therefore say "Have you got the courage of your convictions? Do you believe that aspirin is acting via its clotting effects, for if so you should be considering using over 1000 mg a day? Do you believe that aspirin is likely to work by rebalancing the thromboxane A_2 / PGI_2 equilibrium, for if so you should use 40 mg every second day?"

Old runners can win marathons

While these young runners were scampering round the track an unnoticed veteran was still jogging along the back straight⁵⁰ carrying the national flag of the Netherlands. When global interest in the contribution of coumarin anticoagulation to the secondary prevention of myocardial infarction had waned to vanishing point, the Dutch had kept a routine service going and had then used this to mount a challenging trial. They took 898 patients over 60 who had been maintained on anticoagulants after a proved infarct at least six months before (and the mean interval was actually 5.9 years). They randomised them either to continue anticoagulant treatment or to switch to placebo (so it was a trial of stopping treatment, not of starting it), and they handled the groups in exactly the same way in respect of hospital visits, blood tests, and tablet schedules. Analysed on an intention-to-treat basis (the pragmatic approach), the two-year death rates were: placebo 15.7%, anticoagulation 11.6%, which just fell short of significance. If you are allowed to argue that treatment cannot possibly do any good if the patient is not receiving it (the explicative approach) you can drop the protocol deviants and analyse only the patients still receiving treatment or within 28 days of stopping it. A significant difference in total two-year mortality then emerged (placebo 13.4%; anticoagulation 7.5%).

While the trial presents us with many new questions (and to their eternal credit, the same group are now planning a trial on a starting rather than a stopping basis to try to answer them), the results taken in conjunction with the significant and favourable effect on outcome shown by the randomised trials of the 1960s—especially in patients with heart failure, severe persisting angina, big hearts, or multiple infarcts⁵⁰—show that we probably rejected anticoagulant prophylaxis prematurely. In terms of strength of evidence the contribution of anticoagulants to the secondary prevention of myocardial infarction must be ranked as second to that of beta-blockers, and immeasurably greater than for aspirin, dipyridamole, or sulphinpyrazone.

Beta-blockers: the end of the tunnel

If you begin with doubt you may end with certainty, whereas if you begin with certainty you end with doubt. Our views on the role of postinfarction beta-blockade have gone from "certainty" to doubt to real certainty. For once, we have learnt from our early mistakes, and we can now analyse a group of large, well-conducted trials on an intention-to-treat basis. The topic has been fully reviewed recently in these pages⁵¹⁻⁵³ but my brief requires me to remind you that, while I have no doubt about the validity of the reported reduction of mortality by beta-blockers in the trials, I have grave doubts about the applicability of these findings to the main mass of the population.

Firstly, let us agree on the findings which have been derived by pooling the results of the main late-entry trials (which thereby excludes the early intravenous metoprolol study previously described,²⁰ but which brings in everything else from four to six days and onwards after infarction). The mean placebo death rate was 10.2% and the beta-blocker death rate was 7.5%, a reduction of 26%.⁵⁴ The confidence limits of this reduction are 17% to 35%, so that statistically the true benefit should lie between these values even if it is not actually 26%. Nevertheless, the pooled trials include an agent which is no longer available (practolol) and some trials which are smaller and less convincing than the remainder. My own appraisal would put the needle of the beta-blocker swingometer nearer to 15-20% than to 26%, but the most crucial point to make is that this reduction can be hoped for only in patients who resemble those in the trials.

But do the trial patients really look like the routine admissions to your wards and mine? Firstly, the mean age at death certified in the community as being due to myocardial infarction is 69 for men and 77 for women, and yet most of the trials had upper age barriers that excluded the elderly. If the results are extrapolated into this very large group which has not been scrutinised, as has been done with hypertension in the elderly,⁵⁵ ill effects might easily outweigh benefit. Secondly, the proportion of the infarcts seen by the special trial centres that actually entered the trials was lower than most people realise: in the "beta-blocker heart attack trial" only 23.4% of patients with infarcts were randomised, so are your patients and mine in the 76.6% who were not? The Norwegian propranolol trial, which I nicknamed the "Heineken study," tried to reach those high-risk patients which other trials had not reached. Of 4929 patients considered, only 560 were entered, 1367 being rejected because they were not ill enough and 3002 because they were too ill. So before expecting your patients to conform to their results make sure that they are in the same narrow 11% risk band from whom the trial results derive.

Thirdly, the reasons for exclusion have been incorrectly used to strengthen the case for extrapolating from the trials to the mass of community infarcts, whereas they should be used to urge caution. The most frequent reasons for exclusion in the beta-blocker heart attack trial, for example, were the need for beta-blockers (18%) and contraindications to the drugs (18%). There is no debate about the second group, but a naive argument is being used in respect of the first. The main reasons for needing beta-blockers and thereby being kept out of trials are hypertension and angina, so if you have a patient with an infarct who falls into this category you cannot be sure that he will derive the same benefit as the patients who could actually be included in the trials. They may well do so, but to say that "at least one-third of patients who have survived a myocardial infarct will need a beta-blocker because of hyper-

tension or angina"⁵¹ obscures the fact that while the benefits of treatment can be calculated for people who have had myocardial infarction alone, they cannot yet be calculated for patients after infarction with hypertension and angina because these are the very patients who were excluded from the trials.

Two final points: we should remember that in the countries where the trials were carried out, routine practices differ from our own. For example, the use of digitalis preparations after infarction appears to be much more common than in our wards, reaching 26% in the Norwegian propranolol study. Is the benefit of beta-blockers altered by an interaction with cardiac glycosides? At a more philosophical level we also need to begin to balance benefit against hassle; Geoffrey Rose has pointed out⁵³ that you can only be sure that a man has been saved from coronary disease when he dies of something else! While he remains alive, there is the possibility that death from myocardial infarction is only postponed, not averted. Rose considers that, for timolol to confer one extra year of life on a trial participant, 30 man-years of tablet taking, with the attendant pattern of side effects noted in the trial, would be required. Can we sharpen up our predictions so that we only impose tablet taking, with its constant reminder of illness, on poor-risk people and spare the good-risk survivors, whose subsequent mortality experience differs little from the general community?

The black spot

Simple observations can have considerable prognostic importance; Vedin and colleagues⁵⁶ followed up 292 men discharged from hospital after a first infarct and found that the two-year mortality correlated with the height of the cardiac enzyme activities, the presence of breathlessness or left ventricular failure, heart size, hypertension, atrial fibrillation, and atrioventricular block. Similarly, a cohort of survivors of infarcts followed up for two and five years in Cleveland⁵⁷ showed that hypertension on admission, high blood urea concentrations, atrial arrhythmias, angina, or previous infarction during an eight-hour period of activity just before discharge were all adverse prognostic factors. In Helsinki 28-day survivors aged under 66 were followed up for five years.⁵⁸ The women did better than the men (20.5% mortality *v* 31.6%), second and subsequent attacks were worse than first episodes, and those with transmural infarction fared less well than those with non-transmural (34% *v* 19.7%). Finally, the influence of age on outcome was re-emphasised by Wilcox and Hampton,⁵⁹ who showed that patients aged under 35 with myocardial infarction had an 8% mortality in hospital, rising through the decades to reach 39% in the group aged 75-85.

But these, of course, are passive indices, and a new challenge was offered to clinicians when Thérout and colleagues⁶⁰ took 210 patients admitted to hospital with acute myocardial infarction and carried out a limited treadmill test the day before they were discharged. Patients who showed no ST-segment depression had a 2.1% one-year mortality and a 0.7% sudden death rate compared with a 27% mortality and a 16% sudden death rate in the patients with an abnormal test result. Can exercise testing really detect a 10-fold difference in overall mortality? Two years later, Stang and Lewis,⁶¹ without including the above paper in their reference list, were saying that "exercise testing before discharge in low-risk patients who have had myocardial infarction appears to be a safe way to initiate rehabilitation. It is fair to say that we do not know what to do with all the results."

In the same year the emphasis began to shift; instead of just using the exercise test to put a black spot on patients who were going to do badly, it was being suggested as a way of identifying patients who should be treated for their black spot.⁶² "It seems illogical to consider for coronary arterial surgery all patients in whom angina pectoris develops shortly after myocardial infarction . . . a more reasonable approach would be to pick out those patients in whom ST-segment depression develops during exercise testing, since these are the people most at risk, most likely to have important three vessel disease and so most likely to benefit from coronary artery surgery. However, there is no direct evidence that surgical intervention is beneficial in such patients." The papers have continued to pile up showing that an abnormal exercise response is a bad thing but they do not tell us what we should do about it. A Melbourne group⁶³ showed that abnormal exercise responses were associated with a 33% mortality during follow-up compared with 5% in patients with a normal response, while a second group in the same city⁶⁴ showed that the development of pain on an exercise test before discharge was also a pointer to recurrence and death. Their response to these findings was not, however, to advocate arteriography and surgery but "vigorous secondary prophylaxis," without indicating precisely what this should be.

In 1982 the emphasis is again swinging back towards the use of exercise testing as a prelude to arteriography and surgery, in that Akhras and colleagues,⁶⁵ studying 61 patients with uncomplicated myocardial infarction, reported that exercise testing at two weeks showed 44 with positive responses, of whom 43 had severe coronary disease in vessels additional to those subtending their infarct. Of 17 patients with negative test results, 15 were found to have vessel disease in the infarct area only, so they concluded that "exercise testing has considerable potential for the early identification of multiple-vessel disease in patients with uncomplicated myocardial infarction." In a study which did not use exercise tests, but whose conclusions can perhaps be used to evolve a policy for the future, Sanz and colleagues⁶⁶ catheterised 256 survivors of myocardial infarction at a month and then observed them for 34 months. They found, as already outlined, that the number of diseased vessels and the presence of heart failure were predictors of poor prognosis. They also measured ejection fraction and showed that four-year survival correlated with the ejection fraction at one month. Patients with a normal ejection fraction had a survival rate of 96-100% depending on the number of coronary vessels affected, but this fell to 30% for those with an ejection fraction below 20% who had three-vessel disease. They suggested that surgery is most likely to be offered to patients with three-vessel disease, so "since most survivors of myocardial infarction who are likely to have their lives prolonged by coronary artery bypass surgery are in this group it is reasonable to limit routine coronary arteriography to the 56% of survivors who have ejection fractions between 21% and 49%."

If we use the information from Akhras *et al*⁶⁵ as an additional step in this categorisation, can we argue that on discharge from hospital after myocardial infarction we will do two non-invasive procedures; the one is simple and universally available but the other is not simple so is likely to be limited to major general hospitals. Step 1 would be a limited treadmill test, and those patients with a negative response would be classed as good risk and discharged from follow-up since they have only single-vessel disease. The patients with abnormal responses, indicating additional vessel disease, would then go on to gated blood-pool scanning to measure ejection fraction, and only those with ejection fractions of 21-49% would be considered

for angiography. I would like to see the next generation of clinical trials beginning at this point so that in 10 years we will have definitive answers to the best management for those patients whose hearts are not so bad that they will quickly die but not so good that they will outlive their investigators. Surgical and medical management should be compared, but history suggests that the wish to do something will take precedence over the wish to know.

What should we do?

Having marshalled the facts so that you can judge for yourselves what is likely to still be with us into the twenty-first century and what is likely to be seen as discredited dogma or as quaint tribal physicianly customs, I must now lay my head on the block and offer advice.

(1) When a patient with a suspected infarction arrives in hospital, once it is clear that conditions such as perforation, pancreatitis, pneumothorax, and aortic dissection have been excluded, then the precise diagnosis plays no part in his immediate management. Complex diagnostic measures are not called for, but the acquisition of serial 12-lead electrocardiograms and cardiac enzyme estimations will enable you to characterise the episode retrospectively on the discharge summary. Beware of the patient with previous infarction because his electrocardiogram results and enzyme values may not achieve diagnostic levels, even though his prognosis is impaired.

(2) Patients with suspected infarction should be sited so that if they die someone will notice and will be at hand to support and resuscitate them. For most hospitals such facilities are found in coronary care units, but in hospitals whose staff all have experience in such units an observed bed near the nursing station is just as good. Wherever the patient is cared for, remind the staff that they should look at the patient first and then the monitor, if at all.

(3) Insert a venous cannula and use this plus other routes to ensure really adequate relief of pain, noting as you do so that the amount of analgesic needed may be helping to determine the size of the infarct.

(4) Do not "routinely" put anything into the cannula at the present time but watch out for the next generation of papers about acute beta-blockade, hyaluronidase, and vasodilators, and be prepared to include such agents with your initial pain-relieving cocktail if the evidence swings in their favour.

(5) Do not contemplate acute coronary arteriography or surgery. If your surgical colleagues ask for referrals for acute

intracoronary thrombolysis, either say that you are waiting for the new generation of lytic agents which can be given systemically and which will home in on a thrombus⁶⁷ or say that you will send them suitable patients but they must carry out this procedure without any increase in resources, so that they must place any new activity in competition with elective valve replacements, bypass surgery, and permanent pacing.

(6) Do not forget the veins, so in high-risk patients use prophylactic anticoagulants.

(7) As the patient moves into his predischARGE phase, look at the menu offered for secondary prevention. There is no evidence to justify the large-scale use of aspirin, dipyridamole, or sulphapyrazone; the evidence is much more favourable for anticoagulants, but residual doubters can await the next generation of trials. Beta-blockers are, however, of proved benefit now, but before physicians begin to use them on all their patients I would urge them to remember that in some trials three-quarters of the patients were excluded. They should therefore look at the exclusion clauses carefully and match their own patients with the trial patients. If the patient matches the inclusions he should obviously be given the benefit of the trial regimens, but if he does not then you are on your own, so you must use clinical judgment and be alert for side effects.

(8) Your mind may boggle at the thought of 30 man-years of taking beta-blocker tablets to add one man-year to life. Our patients' minds clearly boggle in respect of other elements of preventive medicine, so perhaps we should insist that patients should display adequate care for their own health by becoming slim, seat-belt wearing non-smokers before we intervene pharmacologically. If you want to render unto Caesar that which is Caesar's by confining your secondary prevention regimen to higher-risk patients there seems little doubt that limited exercise testing before discharge can be a useful discriminator. The role of gated blood-pool scanning with a view to coronary arteriography and subsequent bypass surgery in the high-risk survivor of an infarct is, however, not yet sufficiently clear to form part of your routine management plan.

(9) Be prepared for the advice of today to be the discarded or derided dogma of tomorrow. Remember that every treatment is really an experiment, so try to make it valuable for the future by recording it and preferably by making it part of a properly documented clinical trial so that my successor in the 1990s can offer some real advice.

J R A MITCHELL

Foundation Professor of Medicine,
University of Nottingham,
Queen's Medical Centre,
Nottingham NG7 2UH

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