disorders." In any case, clinicians are unlikely to stop using the word neurosis in their everyday work as a useful collective term for a common group of problems. Indeed, these current disputes about the term neurosis are reminders of a debate some years ago about another controversial word, hysteria. At that time Sir Aubrey Lewis wrote "a tough old word like hysteria dies very hard. It tends to outlive its obituarists."¹⁵ Though neurosis is not as old a word as hysteria, it is likely to prove to be no less tough.

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Regular Review

Back to the future: So what *will* fibrinolytic therapy offer your patients with myocardial infarction?

J R A MITCHELL

"... shall dissolve ... and leave not a rack behind."

The Tempest IV.i.

Our ancestors expected blood to clot when it left the body or when it stayed in the blood vessels after death. They were, therefore, puzzled by the incoagulability of menstrual blood and by Hunter's finding in 1794 that in "animals killed by lightning or electricity ... or who are run very hard and killed in such a state" the blood also remained incoagulable.¹ The next century saw the unravelling of these mysteries and the provision of important clues to an entirely new approach to the management of thrombosis.²

If shed clotted blood is incubated its fibrin coagulum slowly dissolves and the addition of the powerful procoagulant, thrombin, will not produce any further clotting.³ By the beginning of the twentieth century it had been shown that not only was the blood from victims of violent death incoagulable and free of fibrin but that it would also render normal blood incoagulable by digesting its fibrin. This "fibrinolytic activity" was shown to reside in the globulin fraction of the plasma. During this century we have seen the clarification of the lytic pathway by the identification of the inactive β globulin precursor plasminogen, which is capable of being converted to the active serine protease enzyme, plasmin. Plasmin is non-specifically proteolytic and so not only attacks fibrin but also breaks down other proteins, including fibrinogen and members of the clotting cascade. The debates about the part played by "natural fibrinolysis" in the normal economy of the body need not concern us here, but it is still far from clear whether there is a balance between the coagulation and the fibrinolytic pathways which maintains our blood in an appropriate state of fluidity and, if so,

whether disturbances of this balance make any contribution to thrombotic disease. Of more immediate relevance is to ask ourselves whether we can harness the clot dissolving properties of the plasminogen-plasmin system in the treatment of thrombi which have already formed and are about to produce infarction.

Harnessing the lytic system

Early attempts to capitalise on the fibrinolytic system were rather basic; in 1936 Judine "put post-mortem fibrinolysis to practical use by designing a corpse blood transfusion service, the donors being those who had died suddenly and whose blood, consequently fluid, required no anticoagulant."⁴ At the same time Tillett and Garner, at the Rockefeller Institute, were reporting that filtrates of haemolytic streptococci could cause rapid liquefaction of human fibrin,⁴ and by 1945 Christensen and MacLeod had shown that the bacteria were producing an activator of the fibrinolytic system, which they called streptokinase.⁵ We now know that this is a single chain protein with a molecular weight of 48 000 daltons, that it does not activate plasminogen directly but complexes with it, and that this complex is then converted into active plasmin. When we come to consider how to get fibrinolytic activity to the place where we want it (the harmful thrombus) and not to the places which we wish to spare (the helpful haemostatic mechanisms) the relevance of this will become apparent. Streptokinase is antigenic so that its administration may cause fever and allergic reactions, but of more importance is that it stimulates antibody production, so that treatment for more than a few days is impracticable.

Moreover streptococcal infections are common and pre-existing antibodies may block its action. It must be given by intravascular injection and though its own half time is only 30-60 minutes, the effects it produces via the breakdown products of fibrin and the removal of other proteins are much longer lasting.

When methods for measuring fibrinolytic activity became available many tissues were found to contain activators, but the one which initially attracted most commercial attention was the one first observed in urine in 1885 by Sahli³ and subsequently dubbed urokinase.⁶ Prepared initially from specially collected human urine and more recently from human fetal kidney tissue cultures, it is a β globulin consisting of a single polypeptide chain with a molecular weight of 54 000 daltons. Like streptokinase it must be given by intravascular injection, but unlike streptokinase it is not antigenic so produces fewer immediate side effects and may be given for longer periods without stimulating neutralising antibodies. It converts plasminogen to plasmin directly in a two step reaction and has a short half time (five minutes for the urokinase and 10-15 minutes for the plasminogen activator it produces), though it has much longer lasting effects on the clotting proteins.

Hitting the target

The end product of fibrinolytic activation is, then, the serine protease plasmin, which not only attacks the fibrin within an occlusive thrombus but also the much larger pool of circulating clotting factors. An antagonist to free plasmin (α_2 antiplasmin) is present in the blood but it has a limited neutralising capacity, and once this capacity is exceeded the balance swings from "good" fibrinolysis, aimed at a life threatening thrombus, to the induction of a "bad" haemorrhagic state due not only to the destruction of clotting factors but to the antiplatelet effects of the fibrinogen breakdown products. Because plasminogen activator, plasminogen, and the plasmin they produce bind strongly to newly formed fibrin whereas α_2 antiplasmin does not, research workers have exploited this differential affinity for fibrin and for α_2 antiplasmin in two ways.^{7,8} Firstly, they recognised that the preferential attachment of plasminogen to fibrin is through a lysine binding site on the A chain of the plasminogen molecule, which is separate from the serine fibrinolytic activator site. By acylating the latter it could be protected against α_2 antiplasmin as it made its way from a site of injection and through the general circulation to seek out the fibrin being laid down in a developing thrombus. Once attached, deacylation of the plasminogen and plasmin would allow localised lysis to occur without producing any effect on the circulating pool of materials. This "homing beacon" approach is the rationale behind the target seeking acylated streptokinase-plasminogen compounds BRL 26921 (APSAC), which deacylates relatively rapidly (half time 40 minutes), and BRL 33575, which regains its fibrinolytic potential over a longer period (half time 17 hours).

The second approach used the ability of many tissues, including vascular endothelium, to produce powerful activators of the fibrinolytic system.⁹⁻¹¹ Early attempts to harvest tissue plasminogen activator (t-PA) from human tissue cultures proved laborious and expensive, but the material produced had a high affinity for fibrin. The Michaelis constant (K_m) of tissue plasminogen activator for free, circulating plasminogen (65 μ M) was so much higher than for plasminogen which was bound to fibrin (0.14 μ M)

that little conversion of plasminogen to plasmin occurred in the general circulation even when very high plasma tissue plasminogen activator activities were produced. Like acylated streptokinase-plasminogen complexes, tissue plasminogen activator thus seemed to have thrombus seeking properties, but these could not be exploited because of the limitations imposed by its derivation from tissue cultures. The great leap forward—which, as my title implies, may now allow us to exploit the eighteenth century discovery of the fibrinolytic system to modify the clinical course of thrombotic disease—comes from recombinant DNA techniques. By coding mammalian cells for tissue plasminogen activator with a 527 amino acid protein derived from human tissues material identical with human tissue plasminogen activator (rt-PA) can now be produced in large quantities, so we have to ask ourselves what we are going to do with it. Before we can address this question we need to learn from the past, take stock of the present, and only then allow ourselves to look to the future.

Are we now agreed on the target?

When an eminent physicist was asked why the bitter debate between the proponents of the corpuscular and the wave train theories of light transmission had ended he said it was because all the proponents of the corpuscular theory had died. Beliefs often show generation linked swings, and the hard evidence linking myocardial infarction to occlusive thrombosis which had been carefully collected during the 1930s was forgotten by the 1950s such that it was possible to attend conferences on "atherosclerotic heart disease" without hearing thrombosis mentioned. We thought that our Oxford necropsy study had finally re-established the central part played by thrombotic luminal occlusion in the genesis of transmural myocardial infarction,¹² but no sooner was the ink dry on our papers than quaint notions began to emerge suggesting causes of heart attack—thrombus being claimed as a secondary consequence of necrotising myocardial disease or of coronary spasm, while other workers claimed that they found no thrombi, whether primary or secondary, in the hearts they examined. Let us hope that the painstaking work of Davies and Thomas has ended this cyclical "now you see it, now you don't" saga by showing that disruption of plaques accompanied by thrombosis provides a well documented basis for both acute myocardial infarction and sudden cardiac death.¹³

Learning from the past

The only weapons available to attack thrombi in the 1960s were streptokinase and urokinase, and because direct access to the coronary circulation had not become the everyday affair that it is today the lytic activators had to be given by intravenous infusion. The approach to clinical trials was less rigorous at that time, and most studies were too small to allow benefit to be proved or refuted; moreover, they differed widely in their choice of patients, their treatment regimens, their end points, and their pattern of follow up. These disparities have been set out clearly by Yusuf and his colleagues.¹⁴

The only way forward is to mount large scale cooperative studies, and three early steps were taken in this direction. The European Working Party compared intravenous streptokinase with intravenous heparin in 730 patients with acute

myocardial infarction,¹⁵ and the European Collaborative Study randomised 341 patients to either intravenous urokinase plus anticoagulants or to anticoagulants alone.¹⁶ Neither trial produced clear cut results, but the lessons learnt from them about recruitment, analysis, and reporting stood the group in good stead, for its final study of this era set out clearly who had been considered for entry (2338 patients with acute myocardial infarction), who had been studied (315 patients entered within 12 hours; 13.5% of the total), what they had received (intravenous streptokinase for 24 hours plus anticoagulants versus anticoagulants alone), and what end points were used (at 21 days 18 patients treated with streptokinase and 28 control patients had died, but between 21 days and six months only six further patients treated with streptokinase died compared with 20 in the anticoagulant group).¹⁷ How a 24 hour infusion could influence late mortality as well as early mortality puzzled the investigators of the day, but the possibilities of myocardial salvage and of a reduction in infarct size could not be discounted. The fact that lytic treatment was performed with a back up of full conventional anticoagulation should also be noted.

Looking at the present

Two developments have reawakened the previously flagging interest in fibrinolytic treatment. The first is the rapid and widespread development of coronary arteriography, which has made it possible to infuse materials old (streptokinase and urokinase) and new (recombinant plasminogen activators) directly into the coronary tree—but which has also raised the horrendous logistic problem of how to deliver a high technology treatment which is demanding in machinery and manpower to a disease which in Britain alone kills 160 000 people each year.

The impossibility of combating a mass disease with intracoronary infusions prompted the second development, which was to mount larger collaborative trials of intravenous lytic treatment with streptokinase, urokinase, and recombinant plasminogen activators in such a way that modest but technically feasible benefits could be documented.¹⁸ The battles which will dominate our thinking for the next decade are thus intracoronary versus intravenous treatment, and as the weapons which the two sides will be using are the same the armaments manufacturers will be vying with each other to prove that streptokinase kills more enemy troops at less cost than recombinant plasminogen activators or that acylated streptokinase hits its target more effectively than urokinase or its homing derivative, prourokinase.

Does the route matter?

The units which were able to attack occluded coronary arteries directly were also able to show the immediate efficacy of their lytic treatment by serial coronary angiography, but the early reports were based on tiny numbers and concentrated on patency rates rather than on benefit to patients. This important distinction between process and outcome contains the key to what we must ask of the trials we are now mounting. For example, an early report showed that in nine patients intracoronary streptokinase given some three and a half hours after onset reopened the occluded segments in all of them but that in one patient reocclusion occurred.¹⁹ By 1983 the groups were larger, but there were still problems of selective investigation in that in a typical study coronary

arteriograms were performed only in the 24 patients receiving intracoronary streptokinase, showing clearance in 19, whereas the anatomy of the 26 control patients was not described.²⁰ Ventricular function was claimed to be better in the streptokinase group, but once again this was a doctor based end point—a process—whereas what the patient wants to know is whether he will live or die—an outcome. Not all groups agreed that even these process changes were occurring, for another study in 1983 reported that though reperfusion rates were indeed different in patients given intracoronary streptokinase (12 out of 20) and placebo (two out of 20) no beneficial effect was seen on left ventricular function after 12 days and five months.²¹

Later that year the first report of the Western Washington group appeared, in which 250 patients were randomly assigned to intracoronary streptokinase or to conventional coronary care treatment.²² The mean time to random assignment was four and a half hours, and the reperfusion rate in the intracoronary streptokinase group was 68% compared with 12% in the controls, so we were already seeing a less rosy picture than in the earlier, highly selected reports. The 30 day mortality was five out of 134 patients treated with streptokinase (3.7%) and 13 out of 116 controls (11.2%; $p < 0.02$), so for the first time the claim was made that outcome as well as process was being influenced. Last year saw the completion of the 12 month follow up of these Western Washington patients²³ and the reporting of a larger European study.²⁴ In the former the differences seen at 30 days had dwindled into insignificance at one year (11 deaths out of 134 patients given streptokinase (8.2%) as against 17 out of 116 controls (14.7%); $p = 0.10$). In words that will strike terror into the heart of any trial analyst the authors dismiss this negative result by suggesting that “when a minor imbalance in the ejection fraction and infarct location between the two groups was adjusted by logistic regression, the difference in one year mortality became significant.” I am sure others will share my scepticism about such retrospective special pleading.

In the study carried out in the Netherlands, 533 patients admitted within four hours of the onset of symptoms were randomly allocated to conventional coronary care treatment or to intracoronary streptokinase alone in the early stages of the trial but preceded by intravenous streptokinase in the last 117 patients randomised to active treatment. This study thus muddies the waters for comparisons between intracoronary and intravenous regimens, but it did show differences in 28 day mortality (streptokinase 6%; control 12%; $p = 0.03$) and one year mortality (9% v 16%; $p = 0.01$). The differences were greater when the patients in the second phase (who had also received intravenous streptokinase) were considered separately. A price was paid in terms of complications of treatment: 53 of the treated patients bled compared with seven controls and transfusions were needed in 48 patients out of the 269 offered thrombolytic treatment.

In 1983 most people agreed with me that acute intracoronary thrombolysis had “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 5 million, sending their patients with early infarcts to the three investigative centres in Sheffield, Leicester, and Nottingham. There has to be another way.”²⁵

At the same time the impressive patency figures from the intracoronary studies could not be ignored. The year 1983 saw, however, the publication of the first of a new wave of “process” type studies of intravenous streptokinase.²⁶ Given within six hours to 93 patients, 11 of the 26 patients who had early coronary angiograms had their arteries reopened, while in the total group who had angiograms at the fourth week there was an 84% patency rate. By then the investigators were dealing with a selected population of survivors, and there must be uncertainty about their initial coronary state and the rate of spontaneous recanalisation. They did, however, offer a crucial observation that “in 75% of the patent infarct-related arteries the residual luminal diameter was less than 70%,” reminding us of the inability of thrombolysis to modify the disrupted plaques which triggered the occlusion and which provide a powerful stimulus to reocclusion. In 1985 the use of intracoronary streptokinase in a domiciliary first aid care scheme was reported: treatment was begun in 53 patients with a mean of 1.7 hours after onset. At angiography four days later 81% of the arteries which were thought to subtend the infarct were patent.²⁷ Although claims were made for better subsequent myocardial function in patients treated in under one and a half hours, the study was far too small to draw conclusions about outcome.

Direct comparisons

What we urgently need are unequivocal and clear results, in terms of process initially and then in respect of outcome, of direct comparisons between intracoronary and intravenous thrombolysis. At present these are not available. In 1983, 51 patients were randomised at six to seven hours after onset to receive either intracoronary streptokinase (240 000 U over one hour) or intravenous streptokinase (two regimens: 500 000 U in 15 minutes or 1 million U over one hour).²⁸ Patency was restored in 76% of the patients given intracoronary streptokinase, 10% of patients given the lower dose of intravenous streptokinase, and 44% of those given the higher dose of intravenous streptokinase; bleeding needing transfusion occurred in only one patient in each group. This study seems to be offering a choice between a high technology, high patency treatment or a lower technology approach, with a lower but still worthwhile patency rate.

In 1984 a group of 50 patients was randomised to receive intracoronary streptokinase (212 000 U; mean time after pain 4.3 hours) or intravenous streptokinase (administered 2.8 hours after pain by two different regimens: 0.75 million U over five hours or 1 million U over an hour).²⁹ This protocol emphasised the inevitable delay in setting up an intracoronary infusion in comparison with an intravenous one so we must ask whether any theoretical benefits of the intracoronary route are more than outweighed by the earlier attack on the occluding thrombus which the intravenous route permits. Bleeding problems occurred in four of the 27 patients treated with intravenous streptokinase and one of the 23 treated with intracoronary streptokinase. The authors found similar patency rates at angiography during convalescence (intracoronary 76%; intravenous 73%) and only minor differences in electrocardiographic and enzyme patterns which tended to favour intravenous streptokinase.

They concluded, “favourable relative effects were noted on cardiac function, clinical evaluations and hospital course after intravenous streptokinase in early survivors of myocardial infarction and use of an intravenous drug has the advantage of earlier and easier application. Additional studies will be required to address effects on mortality.”

Ancient versus modern

Intravenous versus intracoronary streptokinase is largely a battle within the profession relating to the provision and the value of a high technology approach available to the few or a low technology approach which could be made very widely available. Not so the battle which is now being joined between the old (streptokinase and urokinase) and the new (recombinant tissue plasminogen activator, acylated streptokinase, and prourokinase), which will be a multimillion-pound struggle between the titans of the pharmaceutical industry for a share of a massive potential world market. The first shots were fired in 1984 by a joint Leuven/St Louis group which went on from studies in animals to show that intravenous or intracoronary recombinant tissue plasminogen activator could induce thrombolysis in six out of seven patients with evolving myocardial infarction “without concomitant induction of a systemic lytic state.”³⁰ The bigger guns were fired by the larger United States/Belgian group later that year in its report of 45 patients randomised to receive intravenous recombinant tissue plasminogen activator or placebo plus five additional patients treated with recombinant tissue plasminogen activator.³¹ Of the patients given recombinant tissue plasminogen activator, three quarters showed recanalisation compared with only one of the 14 patients treated with placebo. Furthermore, the remaining 13 members of this placebo group with persistently occluded vessels were then given intracoronary recombinant tissue plasminogen activator and nine of them achieved patency within 45 minutes. Once again there was no evidence of systemic lysis.

Meantime a European based group was adding to the barrage supporting the advance of recombinant tissue plasminogen activator by randomising 64 patients within six hours of onset to receive intravenous recombinant tissue plasminogen activator over 90 minutes and 65 patients to receive 1.5 million U of intravenous streptokinase over 60 minutes.³² The patency rates of the “infarct related” coronary arteries on “assessable coronary angiograms” were 70% and 55%, but shrewd observers will note that the duration of the two treatments was different, and that value judgments about the vessel to be assessed and the quality of the angiograms have crept in. Nevertheless, the old had streptokinase still cleaned out over half the occluded vessels so we now need to ask, How much will it cost to procure the extra 15% patency rate? Mortality was identical in the two groups, and, though the bleeding complications before discharge from hospital were 21 in the recombinant tissue plasminogen activator group and 39 with streptokinase, the similar transfusion requirements (four patients versus five) showed that there was little to choose between the regimens in terms of major bleeding.

As our final volley from the same group we have 129 patients entered within six hours to a randomised comparison of 90 minutes of intravenous recombinant tissue plasminogen activator or of a placebo infusion.³³ The active agent produced a 61% patency rate, but even in the control group 21% showed disobliteration. Bleeding occurred in

11 of the 64 receiving recombinant tissue plasminogen activator and five of the 65 patients treated with placebo. None of these studies has, however, produced a final answer to our ancient versus modern dilemma, so great hopes were pinned on the National Heart, Lung, and Blood Institute's "Thrombosis in Myocardial Infarction Study" (TIMI), phase 1 of which set out to compare the relative thrombolytic potency of intravenous recombinant tissue plasminogen activator and intravenous streptokinase, using as its end point recanalisation of a totally occluded artery 90 minutes after the start of the activator infusion.³⁴ The trial was stopped when 316 patients enrolled within seven hours of the onset of chest pain had been randomised, because of a significant difference in patency rates between the groups; nevertheless, we should note that the number of patients actually compared was only 214, the others having been withdrawn or excluded along the way. Of the 99 patients given recombinant tissue plasminogen activator, the reperfusion rate was 60% compared with 40% in the 115 patients given intravenous streptokinase, both groups receiving their infusions some four and three quarter hours after the onset of pain. The phase 1 study was not intended to study mortality, for which a phase 2 study is being planned. Bleeding rates were, however, similar in the two groups (43% at the puncture sites and 6% from the gut with recombinant tissue plasminogen activator; 47% and 10% with streptokinase), so that the claims that recombinant tissue plasminogen activator is a sniper's rifle while streptokinase is a machine gun need careful scrutiny.

What do we now accept?

Simplistic though the following statements are, not all of them have been previously widely accepted. Firstly, transmural myocardial infarction is a thrombotic problem, so that if thrombolysis can be achieved at the earliest opportunity myocardial damage may be diminished, but the reopened artery will still have an unstable atheromatous plaque which may trigger further occlusions. Secondly, the introduction of fibrinolytic activators into the body can lyse intracoronary thrombi without producing serious systemic lysis. Thirdly, the true differential effectiveness of the route of administration has not yet been determined, though the imperfect evidence does suggest that higher patency rates may be found with the intracoronary route. These differential clearance rates must be confirmed by well designed studies which compare like with like. Finally, as the true comparative merits of regimens ancient (streptokinase) or modern (recombinant tissue plasminogen activator) are not yet clear we will need to evaluate their costs as well as their benefits.

Caveat emptor

What we are looking for has been clearly set out by Sol Sherry, who has spent 30 years unravelling the mechanisms and clinical applications of fibrinolysis.³⁵ We need a simple treatment which can be given by minimally skilled personnel, at the earliest stages of suspected acute myocardial infarction, and which will dissolve the causal thrombus without hazarding the rest of the patient. Sherry is not sure that in recombinant tissue plasminogen activator we have yet attained that ideal. He points out that there are nagging doubts which the present generation of trials has failed to answer:

Comparative efficacy—There has been detailed preliminary study of the most appropriate thrombolytic regimen for intravenous recombinant tissue plasminogen activator, whereas the streptokinase regimens with which they have been compared have not been similarly optimised and have been derived from current practice. Moreover, recombinant tissue plasminogen activator was given for 180 minutes in the thrombosis in myocardial infarction study and 90 minutes in the European study, whereas streptokinase was given for only 60 minutes in each.

Comparative safety—Sherry is not convinced that recombinant tissue plasminogen activator is a "magic bullet" hitting only its thrombotic target and sparing the haemostatic mechanism. He points to the similar major bleeding rates which I have set out above and suggests that when heparin is used, as it was in all the studies analysed, to prevent rethrombosis on the original unstable plaques, then the dose and the nature of the activator have less importance.

Antigenicity—The original tissue plasminogen activator was derived from a human melanoma cell line, but mass production has now switched to using mammalian cells encoded with the tissue plasminogen activator information. Allergic reactions, either during treatment or on retreatment after an interval, will need to be recorded and reported in the studies on recombinant tissue plasminogen activator.

Cost—Urokinase has long been known to be non-antigenic, to be more specific for fibrin, and to have a shorter half life than streptokinase, but because of its cost it has not replaced streptokinase as the most widely used activator. What the cost of saving a life with recombinant tissue plasminogen activator is now or what it will be in 10 years' time cannot readily be answered, but it seems likely to be very substantial. We must therefore ensure that the social and economic costs and benefits of saving that life are going to be fully evaluated.

Verstraete, who like me has lived through the ages of enthusiasm, disillusionment, and now reawakening for anticoagulants and fibrinolysis,^{25,36} reinforces many of these points and a paraphrase of his comments provides an appropriate "state of the art" summary³⁷:

Coronary thrombi can be safely lysed by both intracoronary and intravenous agents; widespread application of intracoronary thrombolysis is not practicable; high dose, short duration intravenous treatment produces acceptable reperfusion rates without major bleeding problems and can be applied in ordinary district hospitals; targeted activators such as recombinant tissue plasminogen activator or acylated streptokinase probably do have advantages, but a full comparative appraisal of costs and benefits must await the results of trials; and early coronary reperfusion may improve myocardial infarction so could resolve my patient's question, "Will I live longer and if so will I be less disabled?"

All the trials reported above have dealt mainly with process and not with outcome, so we must await the detailed analysis of the recently published GISSI study, which randomised 11 712 patients with acute myocardial infarction to receive either intravenous streptokinase or routine coronary care, the 21 day mortality being 10.7% in the treated group and 13% in the controls.³⁸ Other acronymic trials are already nearing completion (the German ISAM with some 2000 patients similarly randomised), are getting under way (TIMI 2 with recombinant tissue plasminogen activator, and ISIS 2 with streptokinase), or are in their final planning stages (ASSET—a joint study of recombinant tissue plasminogen activator versus placebo between Britain and Norway).

Summary

As Verstraete says,³⁷ "To offer the benefit of an effective thrombolytic treatment to a greater proportion of patients as soon as possible after their myocardial infarction, short and simple therapeutic schemes must be developed. The logistics are in favour of an intravenous route for the safest of the thrombolytic drugs. The protective effect of timely reperfusion . . . on short and long term morbidity and mortality will hopefully be established in ongoing trials with sufficient statistical power." We are nowhere near this point at present, but I have no doubt that, just as the 1950s was the anticoagulant decade, the 1960s the decade of enthusiasm for

coronary care and antiarrhythmics, the 1970s of platelet modifying regimens, and the 1980s of coronary artery bypass grafts and β blockers, so the 1990s will be the second age of enthusiasm for a fibrinolytic attack on acute myocardial infarction. When we use a 200 year old observation as a basis for future treatment, we must, however remember Pasteur's dictum, "Keep your enthusiasm but let strict verification be its constant companion."

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