Reviews in Medicine

Cardiology

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Introduction

For cardiology the 1980s was a decade dominated by the original work of two men: Gruentzig who pioneered percutaneous transluminal coronary angioplasty (PTCA) for the treatment of coronary artery disease, and de Wood who with his demonstration that intra-coronary thrombus was the final common path in the development of myocardial infarction, led to the widespread use of life saving thrombolytics. At the end of the decade cardiology is still largely exploring the ramifications of these ideas. It has now been convincingly demonstrated that PTCA works but in a high proportion of cases only for a short while and the search is now on for the answer to the restenosis problem. Thrombolytics also work but not for everyone and different combinations and permutations are being explored. These two subjects comprise directly or indirectly a large proportion of the last year's publications. Of course research continues in many other fields and there have been interesting publications in epidemiology, lipidology, diagnostic techniques and basic science.

We have presented a review of publications that we consider to be significant or of special interest and attempted to highlight their results. We have also pointed out some of their shortcomings and sometimes ponder some of the new questions their findings pose. It is inevitably not a comprehensive review.

What of the next decade? Will we still be in the 'post GISSI-Gruentzig period' or will there be expansion into other fields? Two areas we feel sure will become very important are molecular biology and positron emission tomography (PET). The tools for the molecular biologist are now available and the exploration of their uses has started. Soon we may be able to understand the precise function of vascular endothelium or the cardiac myocytes and maybe have the means of intervening. The relationship between the structure of the coronary arterial tree and functional ischaemia of the myo-

cardium is far from elucidated since we have to date lacked the appropriate tools; PET scanning might be the answer.

Thrombolysis in myocardial infarction

The GISSI study in 1986¹ convincingly demonstrated that mortality in acute myocardial infarction (AMI) was significantly reduced by early administration of intravenous streptokinase. This gave way to a vast number of new questions. Do other thrombolytics work as well? What adjunctive therapy is best? What is the optimum course of action after thrombolysis? How does reperfusion improve mortality? and so on. This last year has seen many publications shedding more light on these questions.

Thrombolytics and mortality

The significant mortality reduction demonstrated by GISSI has been confirmed by the ISIS-2 (Second International Study of Infarct Survival) trial using streptokinase,² the AIMS (APSAC Intervention Mortality Study) using APSAC (anisoylated plasminogen streptokinase activator complex)³ and the ASSET (Anglo-Scandinavian Study of Early Thrombolysis) study using tissue plasminogen activator (tPA).⁴ Although these trials differed in their design, entry criteria, time window from onset of pain to treatment and the adjunctive therapy, there is broad agreement that early (within 6 hours of the onset of pain) thrombolysis with any of the agents yields approximately a 25% reduction in mortality - ASSET 26%, GISSI 20%*, ISIS-2 27%* (* = estimated for 6 hours). AIMS produced a better result with a figure of 47% reduction in 30 day mortality (95% confidence interval 21–65%), but all patients entered into AIMS received a heparin infusion 6 hours after the APSAC and the placebo, and all patients were treated with warfarin for a further 3 months. The AIMS trial was terminated prematurely on ethical grounds and therefore has a relatively small number of patients, 1004, compared with the other trials - GISSI

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11,806; ISIS-2 17,187; ASSET 5,011. These are some of the many features that make genuine comparison of the different drugs impossible from these trials.

Further mortality data come from the latest European Co-operative Study Group Trial⁵ and the German Multi-centre Trial of APSAC.⁶ Both are placebo controlled trials. The German study was designed to assess 28 day mortality and reported a reduction of 56% (12.6% vs 5.6%) but it must be pointed out that the number of patients was relatively small, only 313 patients being randomized. Furthermore, patient inclusion was limited to within 4 hours of the onset of pain, all patients received methylprednisolone, heparin and subsequently warfarin and it was not a double blind trial. Although the European Co-operative study was designed to look primarily at infarct size and left ventricular function it reports early mortality data as well. Using tPA the Group found a reduction in mortality at 14 days of 51% and at 3 months of 36%.

Two small directly comparative trials have been published each comparing tPA with streptokinase and although mortality was not the end point, mortality data have been included. The PAIMS study⁷ with 171 patients reports 44% less mortality with tPA (8.2% streptokinase vs 4.6% tPA) and White *et al.*⁸ with 271 patients similarly report a 49% better mortality with tPA (7.3% streptokinase vs 3.7% tPA). Is it appropriate to publish mortality data from trials not designed for it since the numbers are clearly too small and results suspect? The TIMI (Thrombolysis in Myocardial Infarction) investigators have also published⁹ retrospective, sub group-analysed, 6 and 12 month mortality data from a trial that was designed to compare reperfusion rates between tPA and streptokinase. Despite tPA having twice the 90 minute post-infarct patency rate (62% vs 31%) the reinfarction and mortality rates were very similar. What is striking but not altogether surprising from this analysis is the effect on mortality of 'sustained' LAD (left anterior descending artery) patency regardless which thrombolytic was used. Patients with anterior AMI and a vessel patent at 90 minutes, and still patent at 21 days had a 12 month mortality of 8.6% compared with 19.0% in patients with persistently closed vessels.

That thrombolysis reduces mortality of AMI is in no doubt but which agent is most effective is far from clear. There are now large multi-centre trials directly comparing the effect of the different agents on mortality. The GISSI-2 trial is under way in Italy comparing streptokinase with tPA and ISIS-3 has just started in which three agents, streptokinase, tPA and APSAC, will be randomized.

Thrombolytics and adjunctive therapy

The most striking demonstration of successful adjunctive therapy with thrombolysis in AMI was in ISIS-2 in which patients were randomized to placebo, aspirin alone, streptokinase alone and aspirin and streptokinase combined. The use of aspirin alone at a dose of 160 mg daily from the time of admission reduced mortality by 23% but in combination with streptokinase produced an overall reduction in mortality of 42% from 13.2% in the placebo group to 8% in the treatment group. Additional use of heparin or warfarin was left to individual investigator discretion. Patients entered into the AIMS trial, however, all received heparin and subsequently warfarin; this may be the explanation for the very high reduction in mortality (47%) but since there was no randomization of adjunct this must remain speculative. All trials using tPA to date have involved the concomitant administration of heparin either as bolus or an infusion according to manufacturers recommendations but the possibility of increased bleeding complications has called into question the use of the combination. Topol and the TAMI (Thrombolysis and Angioplasty in Myocardial Infarction) Study Group have published a randomized controlled trial¹⁰ of tPA and bolus heparin versus tPA alone. They conclude that heparin in a bolus of 10,000 units does not facilitate the fibrinolytic effect of tPA but as the authors point out the trial numbers were too small to draw further conclusions that heparin and tPA combined do not achieve more extensive or frequent coronary thrombolysis or increase bleeding complications. They recommend that if heparin is to be used with tPA then it is not required until 2 hours after the administration of the tPA. It is hoped that ISIS-3 will answer some of the questions about adjunctive antithrombotic therapy.

Thrombolysis and left ventricular function

The assessment of left ventricular function is fraught with difficulties in terms of definitions, lack of objectivity and the practicalities of making measurements. Never is it more difficult than when assessing the effect of an intervention in acute myocardial infarction. An adequate pre-intervention investigation is problematic in practical and ethical terms because the need for urgent treatment means there is very little time to organise and perform investigations and any undue delay would be unethical given the evident time-dependent mortality reduction with thrombolysis. Yet having no pre-intervention assessment means huge numbers are required for statistical significance because of the large standard error in any test of left ventricular function after AMI. In what must

surely be the last placebo controlled trial of thrombolysis in AMI, Armstrong and the Toronto (TPAT) group¹¹ overcome these difficulties in reporting the effect of Burroughs Wellcome tPA. This is the first clinical trial of the double chain recombinant tPA to demonstrate anything other than coronary thrombolysis. The authors used radionuclide scanning with technetium-99 in 115 patients to assess global and regional ventricular function 3 to 4 hours after the administration of tPA and again at 9 days. They conclude that there is significant improvement in both global and regional function in the treatment group; baseline ejection fractions being 45.4 ± 1.9 in the placebo group and 49.1 ± 1.6 in the treatment group compared with 47.8 ± 2.2 and 53.6 ± 1.6 respectively at 9 days, an increase in ejection fraction of $5.8\% \pm 2.7\%$. There were no major haemorrhagic complications which may be a reflection of the weight related dosing scheme used in this study and recommended by these manufacturers. The European co-operative study⁶ with primary end points of infarct size and left ventricular function randomized 721 patients to tPA or placebo and assessed ventricular function at a single 14 day (10–22 days) post AMI angiogram. They reported a 2.2% higher ejection fraction in the treated group.

While these two studies demonstrate that tPA preserves left ventricular function after AMI, the earlier report that streptokinase has the same effect¹² has been confirmed by retrospective analysis of the Western Washington Intravenous Streptokinase Trial data¹³ and by Sheehan *et al.*¹⁴ using intracoronary streptokinase. The use of APSAC, however, according to the German multi-centre trial⁶ results in no preservation of left ventricular function.

Two studies directly comparing tPA and streptokinase are at odds. The PAIMS study,⁷ using echocardiography to assess left ventricular function, suggests an increase in ejection fraction between admission and discharge in those treated with tPA but not in those treated with streptokinase, whereas White *et al.*⁸, using 3-week post infarct angiography only, reports no difference between the two agents. The German Activator Urokinase Study (GAUS)¹⁵ which compares tPA with urokinase in 246 patients reports no significant difference in left ventricular function as assessed by ventriculography at 90 minutes, 24 hours and 10 day post-thrombolytic.

These data on ventricular function after thrombolysis are surprising. Why does White⁸ report a greater reduction of mortality in tPA-treated patients than in streptokinase-treated patients yet no difference in the left ventricular function? The same is true of the German multi-centre trial.⁶ Is it that in general the techniques for the assessment of

left ventricular function are too crude to allow appropriate distinctions to be made or do other mechanisms operate? Certainly techniques are inconsistent with different methods and different timing. Assessment by an isolated test some weeks after AMI is probably not good enough, a 'change score' technique must be employed using at least two serial tests. Both White and the German study use only a single assessment of ventricular function a few weeks after AMI and with relatively small numbers this may explain the lack of preservation of ventricular function, but the GAUS study¹⁵ has three serial left ventriculograms to gauge ejection fraction and that trial too shows no preservation of left ventricular function after successful thrombolysis. The more sensitive the test the more likely that changes in left ventricular function will be seen. Regional wall motion studies are more sensitive than global ejection fraction and probably the most sensitive method of left ventriculographic regional wall motion analysis. Sheehans' centre line method was used in the Western Washington paper¹³ and the intracoronary streptokinase paper,¹⁴ both of which did report functional improvement. The suggestion that the more segments of the left ventricle studied the more sensitive the result is further exemplified by two small non-controlled studies of left ventricular function after reperfusion.^{16,17} Both use serial echocardiography, one¹⁶ applying 12 segment regional wall motion analysis and the other¹⁷ using a 16 segment system. Both report significant improvement in left ventricular function.

That reperfusion may operate mechanisms unrelated to infarct size reduction was suggested in a report of experimental work using a rat model.¹⁸ Two groups of rats underwent complete coronary occlusion, one group was re-perfused after 90 minutes and both groups were then examined 6 weeks later at post-mortem. Infarct size and left ventricular cavity size were similar in both groups but the thickness of the healed free wall was significantly thicker in the reperfused group. The significance of such effects is unclear at present but changes in ventricular remodelling may have a bearing on mortality reduction without a detectable change in either infarct size or ventricular function. This so called 'open artery hypothesis' is the subject of the TAMI 6 (Thrombolysis and Angioplasty in AMI) the results of which are expected shortly.

Thrombolytics and arrhythmias

The effect of successful thrombolysis on the frequency of ventricular premature complexes (VPCs) was reported by Theroux *et al.*¹⁹ The treatment group, receiving streptokinase, recorded 21 ± 64 VPCs per hour compared to the controls, receiving

no thrombolysis, who recorded 40 ± 123 VPCs per hour ($P < 0.05$). They concluded that fibrinolysis reduces ventricular electrical instability as assessed by VPC count on Holter monitoring. McComb *et al.*²⁰ tested electrical excitability more thoroughly with programmed electrical stimulation in 92 patients who had received either streptokinase or tPA after AMI. Sustained ventricular tachycardia or ventricular fibrillation was induced in 22% of patients but multi-variate analysis failed to demonstrate that any of the following – thrombolytic agent, successful reperfusion, time to treatment or degree of residual stenosis in the infarct related artery – was an independent predictor of sustained ventricular tachycardia.

New and combined thrombolytics

No trial of thrombolytics in AMI has to date produced greater than 75% patency rate. The reason for this apparent ceiling effect remains unclear but it provides motivation for trying newer thrombolytics and combinations of thrombolytics and antithrombotics.

Low dose urokinase combined with prourokinase achieved a 75% patency rate²¹ and no major haemorrhage in 31 patients. Gold *et al.*²² investigated the effect of tPA and a monoclonal antibody (7E3) directed against the platelet GPIIb/IIIa receptor in a canine model. They showed that the combination of the thrombolytic and the anti-platelet agent accelerated thrombolysis and prevented reocclusion. The same group²³ has also investigated the synergistic effects of tPA and scu-PA (single chain urokinase type plasminogen activator) at a variety of doses in a canine model and demonstrated that the combination allowed a reduction in the total thrombolytic dose but did not prevent early reocclusion. Again reocclusion could be prevented by the addition of anti-GPIIb/IIIa receptor antibody. Use of this specific anti-platelet antibody, which appears to be a potent inhibitor of platelet aggregation, is very exciting and has important implications in thrombolysis and PTCA.

Thrombolysis and PTCA

Since fresh coronary occlusive thrombus largely occurs in diseased arteries successful thrombolysis usually leaves a residual arterial stenosis which it is assumed predisposes the artery to reocclusion. The role of percutaneous transluminal coronary angioplasty (PTCA) in abolishing the residual stenosis after successful thrombolytic therapy is therefore a crucial issue. Should all patients receiving thrombolytics after AMI go on to PTCA and if so when, if not which patients should? Two earlier trials^{24,25} suggest no benefit accrues from immediate angioplasty and this has been supported by the TIMI IIA (Thrombolysis In Myocardial Infarction) results.²⁶

More recently the TIMI IIB²⁷ results have been added and suggest that there is no benefit from delayed (18–48 hours) angioplasty over conservative management. The TAMI 2 trial²⁸ does suggest a benefit from 'rescue' angioplasty in patients in whom thrombolytics fail to achieve recanalization.

What this all means is that early reperfusion followed by sustained reperfusion is what matters, how the reperfusion is attained is immaterial. Since only 75% of patients at best will reperfuse with thrombolytics and of those a proportion will reocclude, it is vital to have a reliable non-invasive technique for establishing whether thrombolysis has been successful. If thrombolysis has failed the patient may then proceed to invasive methods of recanalization.

Thrombolytics and reperfusion

Analysis of the rate of production of creatine kinase-MB (CK-MB) in the venous blood after AMI is a reliable method of determining reperfusion according to two papers. Ong *et al.*²⁹ use a bi-exponential model which they demonstrate fits the physiology in dogs very well and apply it to a patient population. They conclude that the rate constant of the appearance function of CK-MB clearly distinguishes persistent occlusion from reocclusion. Lewis *et al.*³⁰ observe the absolute rate of rise of CK-MB and conclude that with half hourly blood sampling for at least two and a half hours after thrombolytic therapy success or failure can be determined. Both these papers require the frequent sampling of venous blood which is impractical, Ellis *et al.*³¹ describe a method requiring only two blood samples. They examine the rate of production of myoglobin after coronary reperfusion and describe the ratio of myoglobin level at 120 minutes post thrombolysis to myoglobin level at time of thrombolysis. If the ratio is greater than 4.6 then reperfusion has occurred; sensitivity 85%, specificity 100%, predictive accuracy 88%.

Thrombolysis in unstable angina

While it is well documented angioscopically that intracoronary thrombus is largely present in unstable angina, the role of thrombolysis has yet to be determined. deZwaan *et al.*³² have confirmed angiographically that thrombosis is present and that the angiographic appearance may be improved with thrombolytics. Topol *et al.*³³ in a double-blind placebo controlled trial, suggest that in some patients with unstable angina thrombolysis can eliminate the need for PTCA but does not reduce the overall need for revascularisation procedures.

Excellent reviews of aspects of thrombolysis are listed.

Percutaneous transluminal coronary angioplasty (PTCA)

PTCA and results

Four hundred and twenty seven patients who underwent PTCA in 1981 were reviewed by Talley *et al.*³⁴ A very high proportion of the patients (86%) had single vessel disease and 92% had normal left ventricular function. The survival figures (98% cardiac survival) and the lack of symptoms (85%) at 5 years suggest that in this group PTCA is a safe and effective form of treatment. Results from the NHLBI (National Heart Lung and Blood Institute) angioplasty registry which was reopened in 1985 confirmed that primary PTCA results are good even in complicated, older patients with multivessel disease and poor left ventricular function. The NHLBI report³⁵ compares results in 1977–81 with 1985–6 and notes the increasing complexity of disease treated with PTCA but the concomitant increase in primary success rate and similar in-hospital mortality (1%). In a separate report³⁶ the same group compare complications of PTCA between the two periods and note that despite the increased proportion of more complex patients complication rates have decreased or remained the same. This study and the report from Emory University³⁷ reaffirm that the independent predictors of increased mortality in PTCA are poor left ventricular function, female gender, older than 65 years and triple vessel disease.

The Thoraxcenter in Rotterdam has analysed success rates for stable and unstable angina in 840 patients over a 5 year period from 1980–1985.³⁸ Primary success rates were comparable (83% and 87% in stable and unstable groups respectively) as was mortality at 25 months (2.8%), but non-fatal myocardial infarction within 24 hours of PTCA was twice as common in the unstable group (9% vs 4.3%). Long term follow-up revealed a similar event free survival in both groups, 68% in stable and 61% in unstable angina.

While these studies demonstrate the effectiveness of PTCA for most forms of coronary artery disease the crucial question, whether or not it compares favourably with coronary artery by-pass surgery, is still not answered. The results of large randomized trials are eagerly awaited.

PTCA and restenosis

One of the major problems with PTCA is the high restenosis rate which is between 20% and 40% at one year, regardless of operator. Indeed one paper³⁹ suggests that it may be as high as 50% and that it has normally occurred within 3 months of PTCA. A satisfactory solution to this problem is not yet described but anything that reduces res-

tenosis rate at all is very welcome. What predisposes to restenosis is not entirely clear but various independent predictors of restenosis have been identified and it presents a confusing picture. A post-PTCA trans-lesional gradient of greater than 25 mmHg, dissection of the artery and post-PTCA TIMI flow grade 2 or less have been reported by Ellis *et al.*,⁴⁰ but the same group, in another paper,⁴¹ use univariate analysis to identify non-dissection as a predictor of restenosis. Bertrand *et al.*⁴² note that superimposed spasm post-PTCA is associated with a higher rate of restenosis, which is worrying since other authors⁴³ report spasm routinely at the site of dilatation and beyond. Roubin *et al.*⁴⁴ demonstrate that balloon size is not related to restenosis rate. Plaque composition may well be very important in development of restenosis. Potkin and Roberts⁴⁵ in a small post-mortem study propose that lesions with less lipid and low calcium content are more likely to be successful lesions for angioplasty.

The incidence of recurrent restenosis is similar to that reported for initial angioplasty but patients with unstable angina, diabetes and hypertension appear to be at higher risk.⁴⁶ Glazier *et al.* found that the number of balloon inflations predicted the likelihood of a second restenosis.⁴⁷

Anti-coagulants and anti-platelet agents have been tried in attempts to reduce restenosis rate. Ellis *et al.*⁴⁸ randomized patients to heparin or placebo post-PTCA but did not demonstrate any difference in the 6 month restenosis rate. The same applied to the combination of aspirin and dipyridamole⁴⁹ but although the restenosis rate was not significantly different from the placebo group, these agents did significantly reduce the incidence of myocardial infarction related to PTCA.

One encouraging report comes from Dehmer *et al.*⁵⁰ who have published a 59% decrease in the 3 month restenosis rate in patients taking 3.2 g of eicosapentanoic acid daily starting 7 days before PTCA, compared to those randomly allocated to aspirin and dipyridamole. While this seems an exciting result it should be noted that the n-3 fatty acid treated group still had a 3 month restenosis rate of 19%, which is unacceptably high. It would be interesting to know if these studies have taken into account whether or not the patients continued to smoke after PTCA. Galan *et al.*⁵¹ report a 56% higher incidence of restenosis at 6 months in patients that continued to smoke. More aggressive interventional treatment with devices that remove atheroma are now being evaluated (see below) but it has already been demonstrated that there is still restenosis. It is most probable that the ultimate solution to restenosis will be pharmacological and considerable work is being directed at understanding the patho-physiology of the complex process of restenosis. Intimal hyperplasia and medial smooth muscle cell growth are the features apparently

responsible for the recurrent reduction in vessel lumen but understanding the processes that stimulate this proliferation is very much in its infancy. Numerous growth stimulating agents, platelet derived growth factor (PDGF), macrophage derived growth factor (MDGF), fibroblast growth factor (FGF) and interleukin 1 (also secreted by macrophages), have all been implicated and many more are being investigated. It is by the inhibition of PDGF production that the omega 3 fatty acids in fish oils are thought to have their effect.⁵² There is some work to suggest that the physical process of stretching the arterial wall is the responsible trigger⁵³ and this would certainly fit with the observation that balloon oversizing more readily causes restenosis although Lew *et al.*⁵⁴ found that larger balloons did not influence recurrence when treating recurrent restenosis. Most of the research in this field is *in vitro* work or uses animal models of stenosis and restenosis. The advent of atherectomy devices now means that study of atheroma in living patients is possible.

Lasers and atherectomy PTCA

The title of the review article by Waller⁵⁵ 'Crackers, breakers, stretchers, drillers, scrapers, shavers, burners, welders and melters' gives some idea of the large number of new techniques being tried in the search for a definitive non-surgical treatment of coronary artery disease. The impetus for the development of such devices is the persistent restenosis noted in a large proportion of angioplasty patients and the relative difficulty for conventional balloon angioplasty posed by chronic total occlusions.

Although many of these devices have already been described, it is only this year that results of their use in the coronary circulation have been reported. The Rotablator is a rotating flexible shaft (120,000 rev/min) with an abrasive tip of 1–2 mm diameter that was reported in 10 patients to be successful and safe.⁵⁶ The advantage of this system is that it is used over a guide wire, the disadvantage being that it consequently has little application in chronic total occlusion. Restenosis rate is yet to be reported. A similar system was reported from Erbel *et al.* and shown also to be safe and effective.⁵⁷ Stack *et al.* have used an atherectomy device called a transluminal extraction catheter (TEC) which sucks out the debris excised from atherosclerotic lesions by the wire-guided rotatory cutting blade (750 rev/min). Its use in peripheral vessels is reported⁵⁸ but it has since been used successfully in coronary arteries. Another type of atherectomy device is the Simpson catheter. This does not use a guide wire but is like a rotating Crosby capsule sucking atheroma into a side hole in the catheter tip and then slicing it off with a rotating blade within

the catheter tip. There is now considerable experience with this catheter and results are improving.⁵⁹ Whether these devices will reduce long term restenosis rate is still unknown.

Lasers have been used for some time in attempts to recanalise vessels but due to major problems with vessel perforation and thermal damage have not been as promising as anticipated. This year however, coronary laser angioplasty was reported with an over the wire 'cold contact' excimer laser system that avoids both of these complications.⁶⁰ The long term restenosis rates are awaited. There are many other types of laser under investigation, short reviews of the generic problems and future prospects are listed.^{61–63} One of the most important difficulties with lasers is knowing whether one is applying the laser to atheroma or to normal arterial wall, the latter alternative being potentially lethal. One answer to this problem is laser-induced fluorescence⁶⁴ where the constituents of the vessel wall are identified by spectroscopic analysis of the laser-induced fluorescence – normal vessel, lipid and calcium each having characteristic appearances. Thus the ablative laser energy can be directed at diseased areas, sparing the normal vessel.

One cannot discuss the forefront of interventional cardiology without mentioning intravascular stenting. This year there have been a number of reports of intracoronary experience with intravascular stents including over 100 by Sigwart,⁶⁵ while Serruys *et al.* describe their use in coronary by-pass graft stenoses.⁶⁶ New metal stents have been described⁶⁷ and so has an experimental polymeric balloon-implanted endovascular stent.⁶⁸ As a slow release polymer this stent has the potential for localized endovascular drug release as well as having the structural effect on the vessel wall. There is an excellent review on stenting by R.A. Schatz.

New technology for conventional PTCA

Advances in conventional balloon angioplasty have largely been due to improvements in catheter design. Co-axial steerable guide wires made an enormous impact but despite current very low profile balloons there are still problems negotiating very tight stenoses. Thomas *et al.*⁶⁹ published their results using a new balloon with a fixed steerable guide wire, the 'Probe'. The deflated diameter of the 2.0 mm balloon catheter is 0.02 inches and it can accept inflation pressures up to 12 atmospheres. They reported considerable success especially in severe distal lesions and this catheter is now very popular.

An attempt to improve the treatment of complete coronary occlusions has been made with the use of the Magnum wire.⁷⁰ The wire has a shaft diameter of 0.021 inches (0.5 mm) and there is an

'olive'-shaped ball tip 1 mm in diameter. The shape of the tip and the stiffness of the wire enable it to be pushed through vessel occlusions enabling subsequent balloon angioplasty.

For use in high risk coronary angioplasty, where inflation of the balloon causes dangerous ischaemia thus putting the patient at risk and impairing efficacy by limiting inflation times, a new catheter is available. The Stack Autoperfusion catheter⁷¹ has side holes either side of the balloon thereby enabling blood to pass through the central lumen of the balloon catheter from the proximal side of the balloon to the distal artery. Quigley *et al.*⁷¹ consequently report inflation duration times of up to 15 minutes without ischaemic problems.

Myocardial infarction

The best thrombolytic and anti-thrombotic regimen in myocardial infarction remains a matter for debate as does the role of interventional procedures (see above) but there are many other aspects of infarction under investigation.

Secondary prevention

The case for beta blockade reducing the incidence of recurrent myocardial infarction has been made before both for oral and intravenous beta blockers, but the use of other drugs has now been evaluated. Two calcium antagonists, nifedipine and diltiazem, have been the subjects of studies. The SPRINT study (Secondary Prevention Reinfarction Israeli Nifedipine Trial)⁷² investigated prospectively the effect of nifedipine given one to three weeks after acute myocardial infarction on mortality and recurrent infarction. No significant effect was noted. The Multi-Centre Diltiazem Postinfarction Trial⁷³ reports a similar lack of effect on mortality and reinfarction with diltiazem, but they did note a deleterious effect on patients with poor left ventricular function post-infarct. Calcium antagonists should be avoided immediately after acute infarction until more information is available.

One interesting paper on medication in myocardial infarction comes from the Oxford group with another of their meta-analyses. This time it is on the use of the intravenous vasodilators nitroprusside and nitrates. A meta-analysis of ten different trials reveals a significant reduction in mortality with either agent if used in the first week after infarction.⁷⁴ A supporting piece of work has come from Canada⁷⁵ where nitroglycerin infusions, in large enough doses to reduce blood pressure by 10%, were studied for their effect on infarct size. This was a placebo-controlled randomized trial and resulted in a significant reduction in infarct size, infarct extension and mortality in those allocated to the

nitroglycerin group. Why this should be the case is not clear but at first sight it would appear to be the effect of the nitrate to reduce cardiac work. Lam *et al.*,⁷⁶ however, provide another means by which nitrates might benefit the infarct patient. They demonstrate in pigs that nitroglycerin has a potent effect on platelet deposition, a hitherto undescribed and potentially important attribute of the drug.

Non-Q wave infarction (sub-endocardial infarction)

Q wave and non-Q wave myocardial infarction are referred to as transmural and sub-endocardial respectively. Although there is no anatomic correlation to support this the distinction is important because they run different clinical courses and carry different prognoses. If resources for interventional treatment are limited then identification of high risk patients becomes vital in order to achieve maximum cost benefit. Nicod *et al.*⁷⁷ have shown that patients with non-Q wave infarction have a lower in-hospital mortality than Q wave infarction but by one year after the event the position is reversed and mortality is greater than in the Q wave infarction group. This particularly applies in the over 70 years age group. Incidence of non-fatal sequelae including recurrent infarction was the same in both Q and non-Q wave groups. According to Boden *et al.*⁷⁸ the shift in the ST segment on the presenting ECG does not predict which patients will go on to Q wave infarction and the same applies to patients with additional left ventricular hypertrophy on voltage criteria.⁷⁹ However, patients with left ventricular hypertrophy and non-Q wave infarction do have a two-fold increase in the incidence of both reinfarction and death after one year follow-up and therefore warrant identification and intensive investigation in the post non-Q wave infarction period. In another paper⁸⁰ the same author identifies patients with non-Q wave infarction without localizable repolarization changes on their admission ECG as having a favourable short and long term outcome.

The degree of myocardial necrosis in non-Q wave myocardial infarction is often underestimated according to a small but thorough study.⁸¹ Carpeggiani *et al.* demonstrate that conventional enzymatic approach to myocardial damage is inadequate in about half of cases. They point out that myoglobin level provides a much more sensitive indicator of significant damage than creatine kinase or its cardiac specific sub fraction CK-MB.

The use of beta-blockers in non-Q wave infarction appears not to be beneficial according to an abstract from the Beta Blocker Heart Attack Trial using propranolol⁸² but the MDPIT (Multicentre Diltiazem Post Infarction Trial) showed that one year mortality from non-Q wave myocardial

infarction was reduced by 40% in patients allocated diltiazem.⁸³ Since the same group do not demonstrate a one year mortality reduction in Q-wave infarction⁷³ there appears to be a protective effect of diltiazem to maintain the acute post-infarct difference in mortality between non-Q wave and Q wave infarction. This may be the only indication for the use of calcium antagonists following myocardial infarction.

Post-infarction thrombus

Left ventricular (LV) thrombus formation is a well recognized complication of acute myocardial infarction and the question of post-infarction anticoagulation has been moot issue for a long time. The cause of LV thrombus, its natural history and its treatment are the subject of a number of papers. Independent correlates with ventricular thrombus formation after infarction are the degree of decrease in ejection fraction, amount of distortion of ventricular shape and height of the diastolic pressure.⁸⁴ It is not surprising then that patients after thrombolytic therapy do not have less thrombus unless there has been successful reperfusion,⁸⁵ thus presumably preserving left ventricular function and limiting the predisposing factors for thrombus formation. Neither aspirin nor aspirin and dipyridamole prevent the formation of mural thrombus or reduce its embolic potential even if administered within 12 hours of the acute infarction.^{86,87} What happens to the mural thrombus? Without anticoagulation most of them (71%) persist without much change in size or shape for up to two years.⁸⁸ Anticoagulation with warfarin doubles the chance of complete resolution and significantly reduces embolic events. Which thrombi are prone to embolise? A prospective evaluation of thrombus and emboli after acute myocardial infarction using 2-dimensional echocardiography⁸⁹ suggests that mural thrombus which is mobile, adjacent to a hyperkinetic segment and protruding in a number of echocardiographic views is most likely to embolise. This information may help decide which patients should receive anticoagulation after myocardial infarction.

Post infarction arrhythmias

The Cardiac Arrhythmia Pilot Study (CAPS) was a randomized double-blind placebo-controlled trial of anti-arrhythmic drugs in patients 6–60 days after myocardial infarction who had at least ten ventricular premature complexes per hour. The patients were followed for one year. One of the first conclusions that the study provided was that the classification of death as sudden or non-sudden is not equivalent to classifying death as arrhythmic or non-arrhythmic.⁹⁰ Just using time from onset of

symptoms to death (sudden defined as less than one hour) would misclassify 25% of deaths. They have also shown that congestive cardiac failure, while common in the patients studied was not significantly more common in the treated group.⁹¹ The antiarrhythmics being used to suppress the ventricular ectopics were encainide, flecainide, moricizine and imipramine. The only baseline variable, of ten variables investigated by the CAPS group, to bear any relation to the efficacy of anti-ectopic treatment was ejection fraction; patients with higher ejection fractions are more successfully suppressed.⁹² CAPS provided information for the organization and design of the Cardiac Arrhythmia Suppression Trial (CAST) the preliminary results of which have caused some consternation regarding the use of some Class Ic anti-arrhythmic drugs in the post-infarction period.⁹³ The unexpected result of CAST, that flecainide increases mortality in the post-infarction period has led to the recommendation that it should not be used. How it has this effect is unclear. Maybe, as the CAST authors suggest, the observed slowing effect on conduction may predispose to re-entry phenomena. It is also not clear whether this effect is a property of all class I or Ic antiarrhythmics or just confined to flecainide and encainide. Fortunately for manufacturers of disopyramide and propafenone CAST did not use their drugs in the trial and there is no equivalent trial. The final results of CAST are still awaited.

CAPS and CAST have investigated suppression of post-infarction premature beats and their prognosis. The prognosis of primary ventricular fibrillation in post-infarction patients has also been reported.⁹⁴ Perhaps surprisingly these patients do not have any excessive increase in mortality at one year and survival seems to be the same regardless of site of infarction or whether the patients received thrombolytic therapy. The excess mortality in such patients is confined to the in-hospital period.

Which patients are at risk of developing ventricular arrhythmias following myocardial infarction? Two groups have demonstrated the sensitivity of late potential activity in this respect but there is an important lack of specificity.^{95,96} Cripps *et al.*⁹⁷ have combined late potential activity with an exercise test and thus have increased the predictive accuracy. However, these investigations may best be applied to identify low risk patients, they point out that the combination of a negative exercise test and no late potential activity has a 99% predictive accuracy for a low risk of acute phase arrhythmias.

While there is no reliable and safe way of preventing post-infarction arrhythmias at present a glimmer of hope for the future comes from two papers. O'Connor *et al.*⁹⁸ show a protective effect of U-63557A, an experimental agent, against acute

infarction-related ventricular fibrillation in cats by its reduction in thromboxane B2 levels; they also showed a limited effect of the same agent on reperfusion arrhythmias and suggest there are different mechanisms involved in the arrhythmogenic processes. Ruda *et al.*,⁹⁹ on the other hand, have demonstrated a major reduction in ventricular arrhythmias in post-infarction patients using phosphocreatine (Neoton).

Post infarction invasive investigation

Ross *et al.*¹⁰⁰ have published a scheme for the identification of patients at high risk of death within one year after acute myocardial infarction; having designed the scheme they have recorded its impact on one year survival. As a result they recommend that the following categories of patients should undergo invasive investigation with a view to a revascularization procedure. Patients with persistent or recurrent chest pain at rest, those with previous infarction with evidence of left ventricular failure at some time in the early phase, those with a positive early exercise test and in those not exercised an ejection fraction of 20–44%. As far as non-Q wave infarction was concerned they point out that the high risk patients are identified by the other means anyway and do not recommend, as a matter of course, angiography for non-Q wave infarction. This does not answer whether all non-Q wave infarction would benefit from angiography with a longer follow-up than one year.

Epidemiology

Risk factors in coronary artery disease

The Finnish cohorts of the ongoing international study on 25 year follow-up of coronary heart disease risk factors were published recently in the *British Medical Journal*.¹⁰¹ Blood pressure, serum cholesterol and smoking were assessed and the respective hazard ratios for death from coronary heart disease were calculated. There was approximately a two and a half times risk of death if serum cholesterol exceeded 8.4 mmol/l compared to less than 5.2 mmol/l and a similar increased risk from hypertension in the highest quintile (systolic blood pressure greater than 162 mmHg) compared with the lowest (less than 132 mmHg). Smoking 10 cigarettes or more per day increased the hazard ratio by two. Overall the most favourable risk factor profile gave a 50 year old man an estimated conditional probability of death from coronary artery disease in the next 25 years of 12%, compared with 75% with the worst risk factor profile. It will be very interesting to see the results from the

other countries. This study refers to total cholesterol but sub fractions have specific prognostic importance. It has been recognized that low levels of low density lipoprotein cholesterol reduce the risk of coronary artery disease but it has also been suggested that there is an inverse relationship between the risk of coronary artery disease and the level of high density lipoprotein cholesterol. In a statistical review of five epidemiological studies Gordon *et al.* confirm that this is the case.¹⁰² They review the British Regional Heart Study, the Framingham Heart Study, the Lipid Research Clinic Prevalence Mortality Follow-up Study, the Multiple Risk Factor Intervention Trial and the Coronary Primary Prevention Trial. They conclude that the epidemiological data generally support an inverse association of high density lipoprotein cholesterol (HDL) and coronary artery disease event rates, and suggest that coronary artery disease risk decreases by 2–3% for every 1 mg/dl increment in HDL level. This is further confirmed by Livshits *et al.*¹⁰³ in the 20 year follow-up of the Donolo-Tel Aviv prospective coronary artery disease study. Multivariate analysis revealed the percentage of HDL cholesterol to be the single most effective predictor of coronary events surpassing total cholesterol. They conclude that high levels of HDL cholesterol reduce the risk of coronary events in those with higher than normal total cholesterol and low levels increase the risk of coronary events in those with low total cholesterol.

An excellent review of the effect of serum lipid reduction on vascular events is provided by Bilheimer.¹⁰⁴ Low lipid diet remains the initial management in reducing serum lipid levels to limit coronary event risk. Is the lower mortality from ischaemic heart disease seen in vegetarians¹⁰⁵ due to the lower intake of dietary lipid or are there other dietary effects? A paper from the Netherlands¹⁰⁶ reports low levels of vitamin B6 in patients with acute myocardial infarction and discusses the role of B6 deficiency in the pathogenesis of atheroma. They also point out that approximately 20% of the Dutch elderly population is in a B6 deficient state which may well predispose them to coronary artery disease.

Some other interesting epidemiological data have been published recently. Two papers from Utah^{107,108} serve to highlight the importance of family history as an independent risk factor for coronary artery disease and Elford *et al.*¹⁰⁹ report on geographic variations in ischaemic heart disease in Great Britain. This study demonstrated that it is not area of origin and therefore not genetic factors that predisposed to coronary artery disease as much as current place of residence. They did observe the expected difference between north and south.

The type of personality in terms of A or B is relevant to the development of coronary artery disease according to the Framingham Study,¹¹⁰ type A personalities being more likely to develop uncomplicated angina than type B, and modifications to type A characteristics appear to confer protection against coronary death after acute myocardial infarction in patients whose disease is not advanced.¹¹¹ Maybe it is the type B characters who take an afternoon siesta and thereby account for the 30% reduction in incidence of coronary events in the siesta-taking group recorded by Trichopoulos *et al.* in an optimistic paper from Athens.¹¹² This would not be in keeping with the results of the 20 year follow-up of the US railroad study¹¹³ in which a cohort of more than 3000 white railroad workers have been followed and amongst other things had their leisure time physical activity (LTPA) studied. It is clear from this that those people who expended little energy during leisure time were some 30–40% more likely to suffer a coronary death than those very active men who expended about 3600 Kcal/week.

The results of large, long term epidemiological studies are convincingly confirming what has already been suggested and widely assumed regarding the role of risk factors in coronary artery disease. Non-smoking, physically active people with low or normal serum cholesterol and a high percentage of HDL have a considerably decreased risk of non-fatal and fatal coronary events.

Valvular heart disease

Mitral valve leaflet prolapse

Mitral valve leaflet prolapse (MVLP) is commonly diagnosed but it is often unclear which patients are at risk from the condition and its complications of mitral regurgitation, cerebral emboli, arrhythmias and infective endocarditis. Marks *et al.*¹¹⁴ have suggested in a retrospective analysis of 456 patients that those patients with additional mitral leaflet thickening and redundancy of the leaflets have a higher risk of infective and haemodynamic but not embolic complications than those without these features. Wilcken and Hickey¹¹⁵ on the other hand make no anatomical distinction when they identify the risk of haemodynamic complications requiring surgery in the population of New South Wales. They identify men over the age of 50 years as being those most at risk, twice the risk there is for women. The risk increases with advancing age from 50 years on. This group also suggest that the natural history of the condition is in keeping with a 'response to injury' process of progressive degeneration of the valve leading to more and more dysfunction. Peller *et al.*¹¹⁶ interestingly report that

the incidence of MVLP in patients with acute myocardial infarction and chronic coronary artery disease is lower than that in the normal population lending support to the degenerative aetiology. The definitive aetiology of MVLP remains unknown. It does not appear to be related to Marfan syndrome¹¹⁷ and there is no gene defect in genes encoding for collagen fibrillar proteins.^{118,119} Richard Devereux provides a short review on MVLP.

Valvar regurgitation

Deciding when to advise surgery for valvar regurgitation remains one of the most awkward clinical problems in everyday cardiology. Contributing has been the relative difficulty in assessing the severity of the lesion. Angiographic appearances often belie haemodynamic data, both having their own inherent methodological problems, and the conundrum may be further confounded by an asymptomatic patient. This past year has seen a number of publications addressing this problem mainly using colour flow Doppler echocardiography.

Spain *et al.*¹²⁰ assessed mitral regurgitation (MR) and report that the maximal jet area derived from colour flow Doppler imaging showed a good correlation with angiographic grades of MR. It did not show a good correlation with haemodynamic indicators. This result might be expected since, as has been pointed out^{121,122} there are many limitations to the interpretation of jet area as a reliable measure of regurgitation, many of them similar to the limitations of angiography. A more rigorous bi-plane colour Doppler echocardiographic method was described by Bouchard *et al.* to assess aortic regurgitation¹²³ and was shown to correlate well with a radio-nuclide technique. In an *in vitro* study of bioprostheses Vandenburg *et al.*¹²⁴ found that colour flow Doppler, in an arrangement designed to simulate trans-oesophageal echo-Doppler, could accurately localise valvar regurgitation and demonstrated a curvilinear relationship between regurgitant jet area and regurgitant volume. The correlation of jet area with regurgitant volume can be improved significantly if the values are corrected for stroke volume. For assessment of a three dimensional regurgitant jet a two dimensional imaging technique may never provide the answer. Alternative non-invasive methods have been reported. A combination of M-mode echocardiography and continuous wave Doppler with simultaneous electrocardiography and phonocardiography provide a means by which those requiring operation for mitral regurgitation may be identified. Bradley and Gibson¹²⁵ describe this technique and define the time interval between end ejection, derived from the phonocardiogram A2, and the cessation of retrograde mitral valve flow.

They found that an interval of < 55 ms was a powerful predictor of those requiring mitral valve replacement (sensitivity 100%, specificity 86%). Cine magnetic resonance imaging can identify areas of left atrial signal loss which demonstrates a good correlation with severity of mitral regurgitation.¹²⁶

A very simple technique for assessment of the severity of tricuspid regurgitation using two-dimensional echocardiography has been described by Fisher and Goldman.¹²⁷ In analysing 46 patients they found that a tricuspid valve annulus of greater than 3.2 cm in systole or 3.4 cm in diastole predicted moderate or severe valvar regurgitation.

Percutaneous balloon valvotomy and commissurotomy

Often called balloon valvuloplasty it is probably more appropriate to term it mitral commissurotomy and aortic valvotomy since the action of balloon inflation in a stenosed rheumatic mitral valve is to divide one or both commissures – exactly what happens after inflation of a balloon in a calcified stenotic aortic valve is less clear. Letac *et al.*¹²⁸ report that the increase in valve area noted after aortic balloon inflation is due to at least three mechanisms; dilatation of the valve ring by stretching the valve tissue; rupture of the fused commissures; and breaking of calcific deposits in the leaflets.

The results of aortic balloon valvotomy in adults have been reported. Safian *et al.*¹²⁹ published data on 170 consecutive patients and Letac and Cribier¹³⁰ on 218 patients. Despite early significant improvement in transvalvar gradient and valve area increasing from approximately 0.5 cm^2 to 0.9 cm^2 , both groups find a high restenosis rate by about 6 months. An excellent editorial by Block,¹³¹ who himself has a large experience, suggests that the proper place for balloon aortic valvotomy is in those patients who refuse surgery or in whom non-cardiac risk factors preclude surgery as well as a 'bridge' to surgery in those patients whose ventricular function is severely impaired by the valve lesion and in whom improvement of ventricular function will reduce the risk of subsequent surgery. Safian *et al.* also report the beneficial effect of balloon valvotomy on ventricular function¹³² and demonstrate an improvement of mean ejection fraction from $37 \pm 11\%$ before valvotomy to $44 \pm 14\%$ 48 hours after valvotomy increasing to $49 \pm 13\%$ at 3 months.

The relatively limited role for balloon aortic valvotomy applies only to calcific adult valve disease, its role in congenital aortic valve disease is better defined. Sholler *et al.* report a series of 80 congenital aortic valve stenoses treated with balloon valvotomy.¹³³ The results in the short term

compare favourably with surgical valvotomy and the authors highlight some morphological features predictive of outcome. Patients with unicommissural valves are at increased risk of post-valvotomy aortic regurgitation while those with thick valve leaflets do not have such a good reduction in tranvalvar gradient. Keeping the balloon to annulus ratio less than 1 minimizes the risk of significant aortic regurgitation.

Percutaneous mitral commissurotomy (PMC) is increasingly performed and its role as a viable alternative to mitral valve surgery is established. Vahanian *et al.* report their experience in 200 patients using a two-balloon technique in 166.¹³⁴ Their group of patients included those with severe calcification of the valve and the subvalvar apparatus. Eight per cent had residual atrial septal defects and 4% developed severe mitral regurgitation. The authors echo the view that the best results for this procedure are found in those patients who would be good candidates for surgical commissurotomy, i.e., mobile valve leaflets with minimal thickening and minimal calcification and no more than mild mitral regurgitation. A history of cerebral emboli should preclude balloon valvotomy. The follow-up of patients who have undergone PMC is reported from Block's group.¹³⁵ By scoring each patient on echocardiographic features of mitral valve morphology – thickening, rigidity, leaflet calcification and sub-valvar calcification, each 0–4 – they have identified that patients with a score of 8 or less are likely to have a good immediate and long term result compared with those with a score of more than 8. They also identified a high score and the presence of atrial fibrillation as predictors of restenosis.

One of the interesting areas of study that the development of PMC has allowed is the study of atrial natriuretic factor (ANF) in a changing haemodynamic situation. Dussaule *et al.*¹³⁶ and Ishikura *et al.*¹³⁷ both report a direct relationship between the left atrial pressure and the plasma level of ANF but Dussaule *et al.* demonstrate that this relationship does not hold for patients in established atrial fibrillation. They also suggest that cyclic GMP production in the lungs is related to ANF production, (maybe there are ANF receptors in the pulmonary artery), but only in sinus rhythm.

Diagnostic techniques

Echocardiography/Doppler

Two papers suggest non-invasive methods for distinguishing between restrictive cardiomyopathy and constrictive pericarditis, a distinction that is notoriously difficult even with careful and thorough invasive investigation. Morgan *et al.*¹³⁸

report that there are a number of features on the digitised M-mode echocardiogram, the prime one being markedly decreased posterior wall thinning, that identify restrictive cardiomyopathy, while Hatle *et al.*¹³⁹ showed an extra shortening in the tricuspid deceleration time on inspiration measured by Doppler in restrictive cardiomyopathy.

Non invasive assessment of coronary artery disease

Cardiac catheterization remains the definitive technique for the assessment of coronary artery anatomy and the definition of arterial disease. However, the major drawbacks of coronary angiography are its lack of functional information and its necessarily invasive nature. Nuclear imaging, positron emission tomography and magnetic resonance are all being investigated to provide

information complementary to the angiogram and maybe in future to replace it.

Underwood *et al.*¹⁴⁰ describe the creation of a histogram of left ventricular phase values derived from radionuclide ventriculography at rest and during stress. The characteristics of the histogram, in particular the standard deviation of the left ventricular phase, are predictive of coronary artery disease (accuracy 89%).

Iida *et al.*¹⁴¹ have measured absolute myocardial blood flow using HO and dynamic positron emission tomography and were able to detect a decrease in patients with triple vessel disease. Walsh *et al.*¹⁴² go further and have, with a similar technique, described impaired regional myocardial perfusion that correlates with areas of myocardium distal to arterial stenoses.

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