on the patient's own blood has many benefits. Safety is certainly one of them; cost may be another. It's time they were considered seriously.

STUART ROATH

Senior Lecturer in Haematology,
Southampton General Hospital,
Southampton SO9 4XY

- 1 Gonzales JJ, Koch MG. On the role of transients for the prognostic analysis of the AIDS epidemic. *Am J Epidemiol* 1987;126:985-1005.
- 2 Haseltine WA. Silent HIV infections. *N Engl J Med* 1989;320:1487-9.
- 3 Burrows L, Taritter P. Effect of blood transfusions on colonic malignancy recurrence rate. *Lancet* 1982;ii:662.
- 4 Blumberg N, Heal JM. Transfusion and host defences against cancer recurrence and infection. *Transfusion* 1989;29:236-45.
- 5 March J, Donnan PT, Hamer-Hodges DW. Association between transfusion with plasma and the recurrence of colorectal carcinoma. *Br J Surg* 1990;77:623-6.
- 6 Vogelsang GB. Transfusion in associated graft-versus host disease in non-immunocompromised host. *Transfusion* 1990;30:101-3.
- 7 Anderson KC, Weinstein HJ. Transfusion associated graft-versus host disease. *N Engl J Med* 1990;323:315-21.
- 8 NIH Consensus Development Conference Statement. Perioperative red cell transfusion [editorial]. *JAMA* 1988;260:2700.

- 9 Carson JL, Poses RM, Spence RK, Bonavita G. Severity of anaemia and operative mortality and morbidity. *Lancet* 1988;i:727-9.
- 10 Messmer K. Hemodilution—possibilities and safety aspects. *Acta Anaesthesiol Scand* 1988;32:suppl 89:49.
- 11 Baron JF, Vicaut E, Duvelley M. Limits of hemodilution in patients with coronary artery disease. In: Vincent JL. *Update in intensive care and emergency medicine*. Vol 5. Heidelberg: Springer. 1989:32-9.
- 12 Mercuriale F, Biffi E, Inghilleri G. Autotransfusion: a safe alternative. Update in intensive care and emergency medicine. *Update* 1989;39:401-10.
- 13 Wybran J. Prevention of transfusion risks: benefits of an outlook for autologous transfusion. *Dialysis and Transplantation* 1988;17:624-69.
- 14 Kay LA, Noble RS. Autologous blood transfusion for surgery and trauma: benefits and methods. *Haematology Reviews and Communications* 1988;2:305-26.
- 15 Seidl S. Organisation of an autologous predeposit (APD) programme for cardiac surgery patients. In: Messmer K. *Practical methods to avoid homologous blood transfusion. Proceedings of a satellite symposium to the 1st European Regional Congress of the International Society for Blood Transfusion*. Manchester: International Press, 1990:43-6.
- 16 Hunt BJ, Yacoub M. Aprotinin and cardiac surgery. *BMJ* 1991;303:660-1.
- 17 Royston D, Bidstrup BP, Taylor K, Sapsford RN. Effect of aprotinin on need for blood transfusion after open heart surgery. *Lancet* 1987;ii:1289-91.
- 18 Thompson JF, Roath S, Lord R, Chant A, Francis J. Aprotinin in peripheral vascular surgery. *Lancet* 1990;336:911.
- 19 Roath S, Majer RV, Smith AG. The use of aprotinin in thrombocytopenic patients: a preliminary evaluation. *Blood Coagulation and Fibrinolysis* 1990;1:235-7.
- 20 Bolan CD, Alving BM. Pharmacologic agents in the management of bleeding disorders. *Transfusion* 1990;30:541-51.

Aprotinin and cardiac surgery

Reduces perioperative blood loss

Continuing concern over the risk of infection from transfused blood and shortages of donor blood have stimulated interest in pharmacological ways of reducing perioperative bleeding. This is especially true for operations using cardiopulmonary bypass, which require on average five units of blood per patient.¹ Several agents, such as desmopressin and prostacyclin, have been tried but proved disappointing. None have had the efficacy that is now claimed for aprotinin, which recently received its licence in the United Kingdom for use in "high risk" cardiac surgery, having already been licensed for treating life threatening haemorrhage due to hyperplasmaemia.

Royston *et al* unexpectedly found that high dose aprotinin given continuously during cardiopulmonary bypass in "repeat" cardiac surgery reduced intraoperative and postoperative bleeding by 80% and blood consumption eightfold.² Numerous further studies have confirmed their findings. Aprotinin shortens operating times, probably due to a striking reduction in "oozing" from the surgical field.

Aprotinin has been used for various indications since its discovery in 1930.³ Of bovine origin, it is a basic polypeptide of 58 amino acid residues and inhibits serine proteases (a serpin). Unusually for serpins it inhibits a wide range of serine proteases with varying affinity—from plasmin and kallikrein to trypsin and chymotrypsin (which inspired its use in pancreatitis).

How does aprotinin reduce blood loss? During cardiopulmonary bypass kallikrein is formed from its circulating inactive plasma precursor, prekallikrein, during activation of factor XIIc by the artificial surfaces of the bypass equipment (oxygenator and tubing) and by the exposed subendothelium of the surgically cut vessels.⁴ The regimen of high dose aprotinin is designed to maintain plasma concentrations of aprotinin that inhibit kallikrein. As kallikrein is important in initiating the inflammatory response aprotinin reduces the activation of complement, the angiotensin system, and bradykinin and inhibits fibrinolysis and coagulation.

Aprotinin is a potent antifibrinolytic agent, its molar potency in vitro is 100 and 1000 times that of tranexamic acid and ϵ -aminocaproic acid respectively.⁵ Tissue plasminogen activator and factor XIIa are both activators of plasminogen that are formed in excess during cardiopulmonary bypass.⁶ By

inhibiting kallikrein, aprotinin indirectly inhibits the formation of factor XIIa and its release of tissue plasminogen activator (because inhibition of factor XIIa reduces the production of bradykinin, a potent stimulator of tissue plasminogen activator). Any plasmin formed will be neutralised by aprotinin's powerful antiplasmin action.⁷ In vitro studies have also shown that aprotinin inhibits activated protein C,⁸ which is formed during cardiopulmonary bypass and promotes fibrinolysis.⁹

Acquired platelet defects have been incriminated as a major cause of non-surgical bleeding after cardiopulmonary bypass,¹⁰ and this is supported by the finding that platelet transfusions shorten patients' prolonged bleeding time after bypass. High dose aprotinin prevents the prolongation of bleeding time seen after cardiopulmonary bypass without affecting the fall in platelet count, suggesting it somehow preserves platelet function.¹¹ This may relate to its effects on glycoprotein IB, the platelet membrane receptor for von Willebrand factor that is responsible for mediating platelet adhesion and is stripped by cardiopulmonary bypass.¹² Plasmin, elastase, and calpain¹³ are enzymes that can strip glycoprotein Ib receptors from the platelet and are all inhibited by aprotinin.¹⁴

Kallikrein increases the formation of factor XIIa, so that inhibiting the formation of kallikrein with aprotinin inhibits the coagulation cascade: aprotinin is therefore a weak anti-coagulant. Ex vivo tests of the intrinsic system, such as the activated clotting time used to monitor treatment with heparin, are prolonged. This has led to debates about the use of aprotinin with heparin during cardiopulmonary bypass surgery.¹⁵ As aprotinin is a weak anticoagulant could less heparin be used? Until the perioperative and postoperative thrombotic risks of aprotinin are assessed it seems prudent to continue using normal doses of heparin with aprotinin. (This means maintaining the activated coagulation time at 750 seconds.¹⁶) Lower doses of aprotinin than Royston's original regimen given as a single pump priming dose have also significantly reduced perioperative blood loss,¹⁷ meriting further studies of different dosages.

Because aprotinin is a bovine protein, the risk of anaphylaxis exists, especially if previous exposure has occurred—making a preoperative test dose advisable. As

aprotinin is excreted renally lower doses are recommended in renal failure. No studies have yet been published examining the potentially increased risks of postoperative thromboembolic disease and loss of graft patency that may occur with any agent modifying perioperative haemostasis. Until full risk benefit analyses have been performed aprotinin should be used with caution. If, however, these studies indicate little risk, then current studies of aprotinin's use in paediatric and "low risk" cardiac surgery, liver transplantation, and vascular surgery suggest that aprotinin may have wide applications in reducing perioperative bleeding. Its efficacy suggests that the importance of fibrinolytic activation in the pathogenesis of perioperative bleeding has previously been underestimated.

BEVERLEY J HUNT

Senior Research Fellow,
Research Haematology Group,
Harefield Hospital,
Harefield,
Middlesex UB9 6JH

MAGDI YACOB

British Heart Foundation Professor of Cardiac Surgery,
National Heart and Lung Institute and
Royal Brompton Hospital,
London SW6 8HP

- 1 Russell GN, Peterson S, Harper SJ, Fox MA. Homologous blood use and conservation techniques for cardiac surgery in the United Kingdom. *BMJ* 1988;297:1990-1.
- 2 Royston D, Bidstrup BP, Taylor KM, Sapsford RN. Effect of aprotinin on need for blood transfusion after repeat open-heart surgery. *Lancet* 1987;ii:1289-91.
- 3 Kraut E, Frey EK, Werle E. Über die Inaktivierung des kallikreins. *Hoppe-Seyler's Physiological Chemistry* 1930;192:991-1007.
- 4 Tanaka K, Takao M, Yada I, Yuasa H, Kusagawa M, Deguchi K. Alterations in coagulation and fibrinolysis associated with cardiopulmonary bypass during open heart surgery. *Journal of Cardiothoracic Anaesthesia* 1989;3:181-8.
- 5 Dubber HC, McNicol GP, Urtley D, Douglas AS. In vitro and in vivo studies with Trasylol, an anticoagulant and a fibrinolytic inhibitor. *Br J Haematol* 1968;14:31-49.
- 6 Hunt BJ, Cottam S, Segal H, Ginsburg R, Potter D. Inhibition by aprotinin of t-PA mediated fibrinolysis during orthotopic liver transplantation. *Lancet* 1990;336:381.
- 7 Fritz H, Wunderer G. Biochemistry and applications of aprotinin, the kallikrein inhibitor. *Drug Res* 1983;33:479-94.
- 8 Espana F, Estelles A, Griffin JH, Aznar J, Gilabert J. Aprotinin is a competitive inhibitor of activated protein C. *Thromb Res* 1989;56:751-6.
- 9 Tanaka K, Wada K, Morimoto T. The role of the protein C-thrombomodulin system in physiological anticoagulation during cardiopulmonary bypass. *ASAIO Trans* 1989;35:373-5.
- 10 Harker LA. Bleeding after cardiopulmonary bypass [Editorial]. *N Engl J Med* 1986;314:1446-7.
- 11 Bidstrup BP, Royston D, Sapsford RN, Taylor KM. Reduction in blood loss and blood use after cardiopulmonary bypass with high dose aprotinin. *J Thorac Cardiovasc Surg* 1989;97:364-72.
- 12 van Oeveren W, Jansen NJG, Bidstrup BP, Royston D, Westaby S, Neuhof H, et al. Effect of aprotinin on haemostatic mechanisms during cardiopulmonary bypass. *Ann Thorac Surg* 1987;44:640-5.
- 13 McGowan EB, Yeo K-T, Detwiler TC. The action of calcium-dependent protease platelet surface glycoprotein. *J Biochem Biophys* 1983;22:287-301.
- 14 Murphy WG, Moore JC, Warkentin T, Kelton JG. Aprotinin inhibits calpain-induced proteolysis of GPIb on the platelet surface. *Schweiz Med Wochenschr* (in press).
- 15 de Smet AAEA, Joen MCN, van Oeveren W, Roozendaal KJ, Harder MP, Eijssman L, et al. Increased anticoagulation during cardiopulmonary bypass by aprotinin. *J Thorac Cardiovasc Surg* 1990;100:520-7.
- 16 Hunt BJ, Segal H, Yacoub M. Guidelines for monitoring heparin by the activated clotting time when aprotinin is used during cardiopulmonary bypass. *J Thorac Cardiovasc Surg* (in press).
- 17 Carrel T, Bauer E, Laske A, von Segesser L, Turina M. Low dose aprotinin for reduction of blood loss after cardiopulmonary bypass. *Lancet* 1991;337:673.

Coronary bypasses 10 years on

About two in five will occlude

The return of angina comes as a bitter disappointment to patients who have had coronary artery bypass surgery. Ten years ago they believed that they were cured. Their doctors may have had reservations, but they did not know how long the grafts would last. Now we know better, thanks to some prospective studies.

Fitzgibbon and his colleagues from the National Defence Medical Centre in Ottawa have a "compliant" population of military staff, 222 of whom have undergone repeated elective coronary angiography.¹ Rates of occlusion of vein grafts at 1 month and 1, 5, 7.5, and 10 years were 8%, 13%, 20%, 40%, and 41% respectively. The jump at 7.5 years is due to the unplanned inclusion of a group of patients studied again for clinical rather than routine reasons - that is, their angina had returned. Similar results have been obtained in Montreal by Bourassa and colleagues, who reported rates of 3.4% at 2-3 weeks, 10% at 6-18 months, 19% at 5-7 years, and 37% at 10-12 years.² Graft occlusion occurred 2.5 times more commonly after six years than before. Similarly, Lytle *et al* from the Cleveland Clinic found that 36% of grafts were occluded 7.3 years after surgery.³ These authors also report the development of graft stenoses: early studies suggest an incidence of 5-10%, often at the distal anastomosis, but some narrowings are seen in 38% of grafts at five years and 75% at 10 years.¹ Few vein grafts escape disease, but the pathological findings vary with the age of the graft.⁴ Early occlusion is usually due to thrombus, probably resulting from technical problems with the vein, particularly at the distal anastomosis. Fibrointimal hyperplasia occurs next, and conventional atheroma is superimposed some years later.

The main manifestations of these developments are recurrent angina, myocardial infarction, and death. It should be emphasised that surgery improves the 10 year survival of patients at high risk - that is, those with extensive coronary disease and poor left ventricular function.⁵⁻⁷ Mortality in the

surgical groups tends, however, to accelerate after 5-7 years, so that if patients with less severe disease are included no overall benefit is demonstrable. If perioperative myocardial infarction is excluded the rate of subsequent heart attack is lower in the surgical group until five years. Thereafter the incidence rises to 2.4% a year, compared with 1.4% in a comparable group treated medically.⁸ The infarcts, however, are smaller⁹ and less commonly fatal⁸ - no doubt because the grafts and long standing coronary disease have encouraged the development of a mature collateral circulation. Subsequent reinfarction, however, is more likely. Patients presenting with recurrent angina commonly do so with an episode of rest pain some seven years after their operation, a familiar experience that might be termed the seven year glitch.

So what should we do about all this? Firstly, we should remember that surgery for degenerative disease never cures. Bypass surgery should be postponed in those with mild to moderate coronary disease and good left ventricular function. If the coronary arteriogram does not show significant left main stem or three vessel disease medical management can safely be encouraged: extra effort spent on exercise and diet, together with prophylactic nitrates and maintenance β blockade, can be surprisingly successful. We should think twice about surgery for certain patients. Women fare less well, probably because of their smaller stature and vessels¹⁰; younger men, although an apparently deserving group, will have clinically important atherosclerosis of the graft five years later.¹¹ Buying time with angioplasty may therefore be preferable. As for the operation itself, using the left internal mammary artery for the anterior descending graft is clearly desirable because its long term patency is superior (92.5% at 10 years).³ Aspirin also reduces the rate of graft occlusion, halving it at one year in a recent study.¹² Ideally aspirin should be started within hours of surgery, although not before because of the increased risk of bleeding. Despite the many studies of the benefits of aspirin