Review

Transfusion medicine: looking to the future

Lawrence T Goodnough, Aryeh Shander, Mark E Brecher

The evolution of transfusion medicine into a clinically oriented discipline emphasising patient care has been accompanied by challenges that need to be faced as specialists look to the future. Emerging issues that affect blood safety and blood supply, such as pathogen inactivation and more stringent donor screening questions, bring new pressures on the availability of an affordable blood supply. Imminent alternatives for management of anaemia, such as oxygen carriers, hold great promise but, if available, will require close oversight. With current estimates of HIV or hepatitis C viral (HCV) transmission approaching one in 2 000 000 units transfused, keeping to a minimum bacterial contamination of platelet products (one in 2000) and errors in transfusion, with its estimated one in 800 000 mortality rate, assume great urgency. Finally, serious difficulties in blood safety and availability for poor, developing countries require innovative strategies and commitment of resources.

Transfusion medicine has evolved from a mostly laboratory-centred service with a focus on the serological aspects of blood, into a clinically oriented discipline that emphasises patient care. This evolution has taken place over the past 20 years, mostly because of the recognition that HIV and hepatitis C virus (HCV) are transmissible by blood. The resultant emphases on blood safety, appropriate use of blood components, informed consent for blood transfusion, and alternatives to blood have led to substantial advances in reduction of potential risks and complications associated with blood transfusion. Nevertheless, this evolution has been accompanied by challenges for which specialists in transfusion medicine and their clinical colleagues must chart an uncertain course into the future. Here, we overview selected issues, and discuss how their resolution could be turned into opportunities for the future.

Blood centres

Blood availability

Sporadic shortages of blood and blood products (eg, packed red cells, platelet products, albumin, intravenous immunoglobulin, and clotting factor concentrates) are potentially life-threatening occurrences. Such shortages have been attributed to various causes, including disruptions in production, increasingly strict criteria for donor deferral, product recalls, increase in use (including off-label), and possibly supply disruptions because of stockpiling or other market issues. Additionally, the ability of blood centres to supply blood in response to acute crises has assumed particular importance after the Sept 11, 2001, terrorist attacks in the USA.[1,2]

In an attempt to anticipate and manage such shortages better, various organisations and government agencies have started to track production and use of such products. For example, in the UK, the Blood Stocks Management Scheme was established in 1997 as a collaborative venture between the National Blood Service and the hospital sector to understand and improve management of supplies.[3] This system uses web-based submission of data and instant graphic feedback and was implemented in April, 2001. As of February, 2002, 167 (54%) of hospitals served by the National Blood Service were tracking 1·44 million red cell units/year (65% of National Blood Service issues).[3] In the USA, the Department of Health and Human Services began in August, 2001, to monitor the ability of the US blood supply to meet demand.[4] This system monitors three sentinel community blood services and 26 sentinel hospital transfusion services, which account for about 10% of the US inventory of red blood cells and platelets.

A comprehensive national survey of blood collections and blood transfusions in the USA has been done by the Center for Blood Research from 1982 to 1994, and subsequently by the National Blood Data Resource Center. Blood transfusion and collection activities peaked in 1986, and then declined.[5] However, blood transfusions and collections increased from 8·0% in 1997 to 10·2% in 1999; Quikount surveys from the National Blood Data Resource Center of US blood centres (80·4% response rate) in 2000 estimated that 12·54 million allogeneic blood units were transfused—a yearly increase of 4–5% from 1999 (M Sullivan, National Blood Data Resource Center, personal communication).

Search strategy and selection criteria

We searched the National Library of Medicine (NLM) database by the NLM Gateway web site for the past 5 years, and from review of the authors, titles, abstract, and source location, articles in full were selected for further examination. This search was done within *The Lancet's* guidelines for articles in its Seminar format. Medline searches were done with Ovid Technologies, Version 4.4.0, through the University of North Carolina Health Sciences Library. We searched the internet using the Google search engine. Specific searches were done at the http://www.fda.gov/cber/index.html, http://www.cdc.gov/ and http://www.who.int/home-page/ sites. References were selected according to the authors' identification of relevant topics for the review.

Lancet 2003; **361:** 161–69

Departments of Medicine, and Pathology and Immunology, Washington University School of Medicine, St Louis, MO, USA (L T Goodnough MD); **Department of Anesthesiology, Mount Sinai School of Medicine, New York, and Department of Anesthesiology, Critical Care and Hyperbaric Medicine, Englewood Medical Center, Englewood, NJ** (A Shander MD); **Department of Pathology and Laboratory Medicine, University of North Carolina School of Medicine, Chapel Hill, NC** (M E Brecher MD)

Correspondence to: Dr Lawrence T Goodnough, Washington University School of Medicine, Division of Laboratory Medicine, Box 8118, 660 S Euclid Avenue, St Louis, MO 63110, USA (e-mail: goodnough@labmed.wustl.edu)

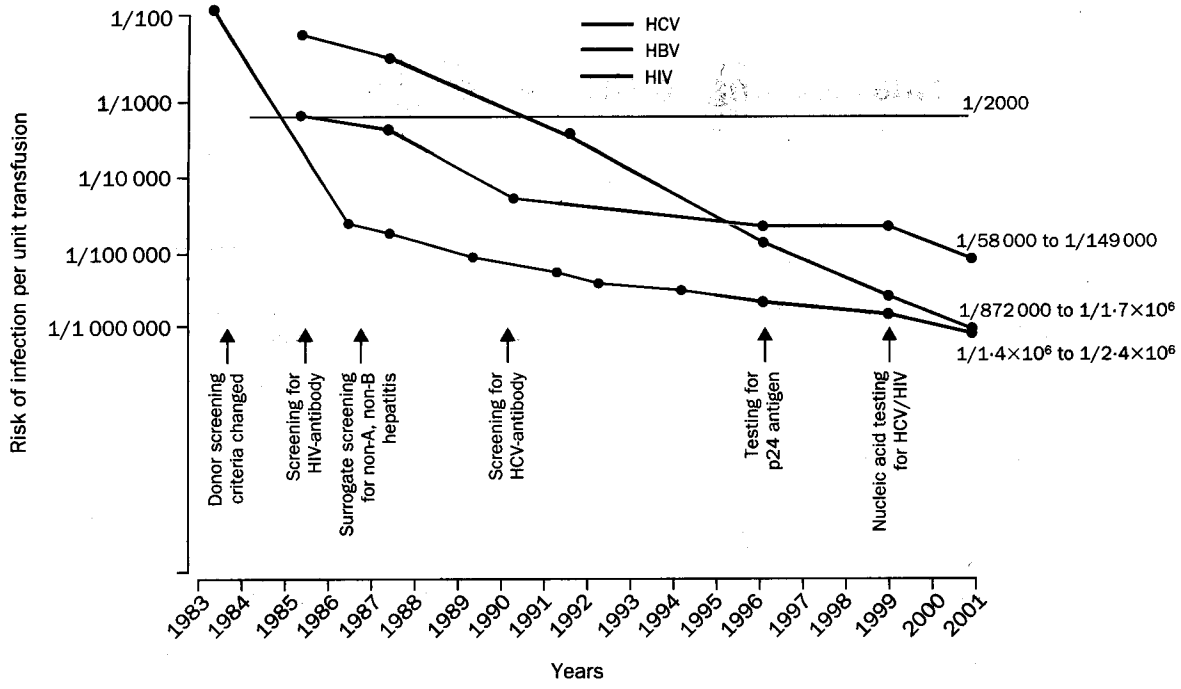

Figure 1: **Risks of transfusion-related transmission of HIV, hepatitis B virus (HBV), and hepatitis C virus (HCV) in the USA**
Every unit is exposure to one donor. Modified from reference 11, with permission of the publisher.

Allogeneic blood collections in 2000 were 13·37 million units—a surplus of 6·2%. This fractional surplus has diminished from the 7·4% of untransfused units in 1997[5] because of increased demand for blood and loss of donors. Current estimates, modified by events of Sept 11, 2001, predict that US blood collections in 2001 surpassed 15·0 million units.

Faced with future prospects of acute demand for blood supplies or transient decreases in donor collection, blood centres and transfusion services have begun to reexamine their approach to inventory reserves. In the USA, there is much heterogeneity in how reserves are maintained. Within the American Red Cross (which supplies about half of all blood products in the USA), a 3–4 day supply of red blood cell products is typical.[6] Some independent centres allow for higher reserves. For example, the Oklahoma Blood Institute typically has a 14–17 day supply of red cell product.[7] Use of frozen red cells as a hedge against inventory shortages has generally not been practical because the shelf-life of thawed units is only 24 h. However, an automated, functionally closed system (ACP 215, Haemonetics, Braintree, MA, USA) for the glycerolisation and deglycerolisation processes has now become available and allows for a 2-week post-thaw shelf life.[8] With the availability of such a system, the Oklahoma Blood Institute plans to increase its available red cell inventory to 21–24 days, with a rotating frozen red cell reserve of 2000 units.[7] Similarly, the Yale-New Haven Hospital transfusion service plans to freeze 200 units of red cells with this new system to provide them with a 3-day supply of blood products for emergencies.[9]

Because of the time needed for blood processing and testing, it is the blood donated before a disaster that is transfused for lives placed at risk. It is now apparent that after disasters (human or natural) in the short-term, on-hand blood supplies are adequate and can be rapidly mobilised over great distances.[1] The wave of donations after the Sept 11, 2001 attack overwhelmed the donor system in the USA, and few of the new donors have become regular donors.[2] The challenge is to successfully recruit and maintain an adequate blood supply before the blood is needed, not after.

Blood safety

Blood centres have now implemented nucleic acid testing of minipools (16–24 donation samples/pool) from blood donations to reduce HIV and HCV transmissions during the infectious window period (before serological conversion). Current estimates of the risk per unit of blood in the post-nucleic acid testing era are 1 in $1·4\times10^6$ to $2·4\times10^6$ for HIV and 1 in 872 000 to $1·7\times10^6$ for hepatitis C virus.[10,11] Figure 1 shows the changes in risk of transfusion-related transmission of HIV, hepatitis C, and hepatitis B in the USA as a result of the various strategies implemented. In the USA since 1999, over 25 million blood donations have been screened. To date, three cases of an apparent HIV transmission by a unit negative by both minipool nucleic acid testing and HIV serology (antibodies against HIV and antigens to HIV p24) have taken place,[12] and one documented case of apparent hepatitis C transmission by a unit negative by both minipool nucleic acid testing and hepatitis C serology has been reported from Germany.[13] These cases suggest that adoption of single donor nat testing will be likely.

At present, the greatest risk of transfusion-transmitted disease is bacterial contamination of platelets. Unlike viruses, bacteria can proliferate from low concentrations (<1 colony-forming units/mL) at the time of collection to very high concentrations ($>1\times10^8$ CFU/mL) during the liquid storage period of blood components. Since platelets are stored for up to 5 days at 20–24°C, they constitute an excellent growth medium for bacteria. Culture surveillance suggests that bacterial contamination of platelet concentrates and apheresis platelets occurs in about 1 in every 2000 units.[14–16] Although the true prevalence of severe episodes of transfusion-associated bacterial sepsis is not known, it is estimated to occur with a quarter to a sixth of contaminated transfusions.[17–19] With

4 million (1 million apheresis platelets and 3 million platelet concentrates) platelet units transfused yearly in the USA alone, it would be expected that 2000 to 4000 bacterially contaminated units would be transfused and be associated with 333 to 1000 cases of severe and possibly fatal sepsis. Pooled platelet concentrates have a higher risk than apheresis platelets (a function of the number of units pooled, reflecting the increased donor exposure and number of phlebotomies required to obtain the products).[20]

Recent reports from Europe and North America have advocated use of automated liquid media culture systems for testing of platelets to reduce the risk of bacterial contamination.[21–25] Culturing of platelets is mandatory in Belgium (Flemish Red Cross) and the Netherlands. Although not mandatory, platelets are also cultured in most blood centres in Sweden, Norway, and Denmark and in selected sites in the UK, Germany, Canada, and the USA. Culturing is typically done after some storage time has elapsed (eg, 1–2 days) to allow for bacterial growth to optimise detection. In some cases, such culturing is used as a rationale to extend the shelf life of platelets to 7 days.[21–27]

Another promising approach is pathogen inactivation (eg, psoralens with ultraviolet irradiation), with the potential to eliminate viral and bacterial contaminants in platelets.[28] However, these techniques have difficulty inactivating spore-forming bacteria (eg, *Bacillus* spp).[29] Another concern is that such processing can lead to decreased platelet recovery and in-vivo survival (thereby leading to the need for increased platelet transfusions).[30] This occurrence was seen in the US clinical trial[31] with apheresis platelets, with lower post-transfusion corrected count increments and increased platelet transfusion requirements for maintenance of haemostasis, when compared with untreated platelets. Additionally, potential concerns about mutagenicity and teratogenicity of such compounds, along with costs and limited availability (for example, the pivotal US phase-3 trial for platelet products was done with products derived from apheresis technology from one vendor) leave the eventual role of this technology uncertain.

Donor screening

Donor-deferral questions remain important complementary methods for increasing transfusion safety, especially for diseases for which routine laboratory testing is not done. Deferral policies for selected diseases are being re-evaluated. The US Food and Drug Administration (FDA) revised deferral criteria for malaria risk in 1994,[32] but another revision is being considered; 103 cases of transfusion-transmitted disease were reported to the US Centers for Disease Control from 1958 through 1998, with an estimated occurrence of 0·25 per million units transfused.[33] Two-thirds of these diseases arose in donors who should have been excluded under current screening criteria, but the remaining third were from donors whose last travel exceeded the time limits (a minimum of 3 years for immigrants or residents from endemic regions) in the FDA's guidelines.[34] Transfusion-transmitted malaria is similarly a potential infectious threat in Europe.

Chagas disease (*Trypanosoma cruzi*) is endemic in many parts of Central and South America. Transfusion-transmitted Chagas disease is a major concern because *T cruzi* establishes a chronic, asymptomatic carrier state in most infected persons (table).[35,36] Donor history screening for risk factors associated with *T cruzi* infection have poor specificity; in one study, 39·5% of donors at a Los Angeles hospital were judged to be at risk of *T cruzi* infection, and of these, one in 500 were confirmed antibody positive.[37] To date, seven cases of transfusion-transmitted and three cases of transplant-associated Chagas disease (from one organ donor) in the USA and Canada have been reported.[38,39] Although donor screening for *T cruzi* antibodies is important in endemic conditions in Latin and South America (table), there is no direct evidence to suggest that introduction of routine donor screening for antibodies to this organism in all donors would measurably improve the safety of the USA blood supply. A pilot programme to screen and test blood donors for *T cruzi* infection is underway in Canada.

	Number of blood donations	Seroprevalence in blood donors	Screening coverage (%)	Potential cases
Country				
Chile	220 686	9·7%	79·8%	16
Colombia	422 300	11·1%	99·9%	2
Costa Rica	58 436	25·7%	6·9%	487
Ecuador	110 619	1·3%	72·3%	9
El Salvador	34 091	19·0%	100·0%	0
Honduras	27 963	11·9%	99·0%	1
Nicaragua	46 539	3·9%	62·1%	21
Panama	42 342	NA	NA	NA
Paraguay	39 904	37·7%	100·0%	0
Peru	203 690	2·0%	60·0%	36
Uruguay	115 490	6·5%	100·0%	0
Venezuela	262 295	7·8%	100·0%	0

Data are from reference 37. NA=not available.

Estimates of blood donation, seroprevalence, screening coverage, and number of potential cases for *Trypanosoma cruzi* in Latin America (1997)

Transfusion-associated babesioses is another example of a transmissible zoonotic disease. Red cells and platelets prepared from asymptomatic donors have been implicated in more than 30 transfusion-transmitted cases. Asplenic, elderly, or severely immunocompromised patients are at the greatest risk of developing haemolytic anaemia, coagulopathy, and renal failure. At present, no test is available for mass screening to detect asymptomatic carriers of babesia species.[40]

Donor referral criteria to deal with the potential problems of Creutzfeldt-Jakob disease (CJD) and variant CJD (vCJD) were implemented in 1987. Although CJD has been transmitted from human to human by transplantation of dura matter or cornea, injection of pituitary growth hormone, or reuse of electroencephalograph electrodes,[41] no cases of transmission by blood transfusion have been reported. Results of newer epidemiological studies[42] confirm earlier studies that failed to show a link between transfusion and transmission of CJD. Despite concerns about potential transmission of circulating prions, there is an emerging consensus that CJD is rarely, if ever, transmitted by blood transfusion. Strategies implemented such as donor deferral schemes, universal leucoreduction, etc, are therefore considered precautionary.

Deferral of donors who have spent longer than 6 months in the UK from 1980 through 1996 was implemented in the USA in April, 2000, in a pre-emptive effort to keep the potential risk of vCJD to a minimum while avoiding disruption of the blood supply. As of October, 2002, more than 137 patients, mostly in the UK (128), but also six patients in France, and one in Italy have been diagnosed with vCJD. As a further measure to reduce the potential risk of vCJD by transfusion, new donor deferrals were implemented in the USA in October, 2002: cumulative time spent from 1980 to present in the UK longer than 3 months, in Europe longer than 5 years,

or on a US military base in Europe longer than 6 months. These criteria are estimated to reduce by 90% the total donor person-days of exposure to the putative agent of vCJD, with an estimated loss of about 5% of the US donor pool.[43] The effect of these enhanced donor-screening measures is expected to be most severe in the metropolitan New York City region, which in the past has derived about 25% of its blood inventory via importation from the European Union.

Transfusion services

Errors in transfusion medicine

Errors are inevitable in any process, and mistransfusion resulting in death has been recognised for half a century.[44] The mistransfusion rate (blood transfused to other than the intended recipient) is about one in 14 000 units in the USA[45] and one in 18 000 in the UK.[46] About half the errors occur in the clinical arena (incorrect identification of the recipient to the blood unit, phlebotomy errors, failure to recognise a transfusion reaction), and about 30% in the laboratory.[47] A similar error rate (one in 17 000) has been identified for autologous blood units in Canada.[48] One in 33 000 units are ABO-incompatible because of error, half of those are associated with a transfusion reaction, and about 10% are fatal.[45] The frequency of death due to ABO-error is one per 800 000 blood units,[47] compared with about one per 2 000 000 transfusions for transmission of HIV or hepatitis C.[10]

The current data probably underestimate the magnitude of non-infectious serious hazards of transfusion, since they are derived from passive haemovigilance reporting systems. In the USA, only fatal transfusion reactions have been required to be reported to the FDA since 1975. Nevertheless, the FDA reported transfusion-related death rate was more than twice that due to all infectious hazards combined, and the UK surveillance system reported an adverse event rate attributed to mistransfusion that was 10 times higher than the rate attributed to infectious-disease transmission.[49]

A system of voluntary, confidential, non-punitive reporting is believed to be an important approach to improving transfusion safety, similar to a quality improvement system for safety existent in the airline industry.[50] A medical event reporting system (MERS) for transfusion medicine now being piloted in several locations.[51] As well as haemovigillance schemes in the UK and in France, the MERS strategy implements an internal tracking system to identify and investigate errors (sentinel events, such as mistransfusions that result in haemolysis or death) and precursor events (near misses, such as phlebotomy sample errors) facilitating causal analysis so that action can be taken to prevent recurrence. Additionally, because 61% of errors originate in clinical, patient-related settings,[52] processes to ensure identification of patients with blood samples and blood units need to be considered as an adjunct to existing policies and procedures for administration of blood. These include blood bag locking devices[53] and bar codes for patient and blood unit identification.[54] Finally, a national voluntary, confidential, and non-punitive reporting system developed in partnership with regulatory agencies should be developed in parallel with local, operational systems such as medical event reporting systems for transfusion medicine.

Undertransfusion

Although much attention has been paid to the risks and complications associated with blood transfusion, much less is known about the benefit of blood transfusion, or conversely, the risks associated with (untreated) anaemia.[55] The estimated risks of a blood transfusion are quantifiable and can be communicated to patients, but the risks of anaemia (in the absence of a blood transfusion) are poorly understood and cannot be accurately conveyed.

Anaemia has traditionally been regarded as an abnormal laboratory value, rather than as a serious disorder associated with, or probably the cause of, adverse clinical outcomes. By contrast with treatment algorithms or recommendations that have been developed for other disorders such as hypercholesterolemia or hypertension, guidelines for management of anaemia have been developed for only a few patients. The relation between anaemia and morbidity[56–59] and mortality[60–62] has been established best in patients with chronic kidney disease, leading to development of guidelines that these patients be maintained at haemoglobin concentrations between 110 g/L and 120 g/L.[63]

Information about the effect of anaemia on mortality is becoming increasingly apparent in patients in other clinical settings. A growing body of evidence suggests that anaemia affects the outlook in patients who have congestive heart failure or who have ischaemic heart disease. Two large observational studies[64,65] noted an association between haemoglobin concentrations of 95–100 g/L and increased mortality in patients with cardiovascular disease, suggesting that such patients did not tolerate anaemia as well as those without known cardiovascular disease.

Investigators of a randomised trial[66] in patients with moderate to severe congestive heart failure (New York Heart Association class III to IV) assessed whether treatment of anaemia affected clinical outcomes. Over 8 months, haemoglobin concentrations in the treatment cohort increased from 103 g/L to 129 g/L, with improved left ventricular ejection fractions, reduction in diuretic therapy dose, and reduction in hospital days compared with controls. 25% of the control group died during the study interval, compared with none in the treatment group.

Results of a retrospective observational analysis[67] of 78 974 elderly patients admitted with acute myocardial infarction in the USA showed that in those with admission packed-cell volumes of less than 33%, blood transfusions were associated with significantly lower 30-day mortality. In the absence of prospective data or other data to the contrary, many lives could be saved when patients who present with acute myocardial infarction are maintained at packed-cell volumes of greater than 33%.[68] For the first time, data are emerging that undertransfusion can lead to adverse outcomes.[69,70]

Guidelines for management of anaemia need to be developed in several clinical settings. The request for applications by the US National Institutes of Health to establish a clinical trials network in transfusion medicine[71]

Panel 1: Examples of biotechnology products in transfusion medicine

Erythropoiesis stimulants	**Haemostasis**
Erythropoietin	Recombinant factor VIIa
New erythropoietin stimulating factor	Recombinant factor VIII
	Recombinant factor IX
Artificial oxygen carriers	**Anticoagulants**
Haemoglobin solutions	Antithrombin III
Perfluorocarbons	Activated protein C

Panel 2: **Potential characteristics of artificial oxygen carriers**

Advantages
Stroma-free
Not antigenic
Oxygen unloading devoid
of 2,3-diphosphoglycerate effect
P_{50} about 20 mm Hg (normal haemoglobin P_{50} 27 mm Hg)
Pathogen inactivation
Size about 1 μm
Possibility of unlimited availability
Extended shelf life >2 years
High oncotic properties
Altered oxygen affinity and unloading characteristics (bovine)

Limitations
Short intravascular life 1–2 h
Possible renal toxic effects
Negative inotropic effect
Possible pulmonary and
systemic hypertension
Possible immune suppression
Possible anaphylaxis
Limited resuscitation ability limited to haemoglobin 50–70 g/L equivalent Interference in some laboratory determinations

is an opportunity for clinical studies to answer these and other important questions.

Emerging technologies

More and more biotechnology products are becoming available as alternatives to blood transfusion,[72] some of which are listed in panel 1. Stimulants of red blood cell production include recombinant human erythropoietin and an altered erythropoietin molecule (new erythropoietin stimulating factor), which has a longer half-disappearance time. Recombinant factor VIIa is now approved for patients with haemophilia who have inhibitors,[73] but there are also ongoing clinical trials of this haemostatic agent in patients without pre-existing coagulopathy in perioperative haemorrhage, in those with thrombocytopenia after peripheral stem cell transplantation, in those undergoing liver transplantation, and in trauma patients. The ability of factor VIIa to activate factor X directly on the platelet membrane surface and restrict its activity to localised regions of tissue factor makes this product potentially useful in patients with substantial haemorrhage, with or without the presence of a coagulopathy.

Artificial oxygen carriers

Progress in development of artificial oxygen carriers has accelerated.[74,75] Potential advantages for cell-free haemoglobin solutions and perfluorocarbon emulsions (as synthetic oxygen carriers) are listed in panel 2. Possible disadvantages of such products include interference with interpretation of some laboratory tests,[76] and their short time in circulation (24–48 h).[77] One potential difficulty associated with haemoglobin solutions is vasoconstriction, a consequence of their ability to bind nitric oxide.[78] The nitric oxide binding properties of haemoglobin are thought to be responsible for the gastrointestinal discomfort observed in clinical trials of some products.[75]

The vasoconstrictive effect could also be explained by autoregulation, since small molecules, such as haemoglobin solutions, overdeliver oxygen to vessel walls.[79] Results of one study[80] assessing oxygen delivery after administration of clinically relevant doses of a haemoglobin solution to anesthetised surgical patients showed that the ability of the haemoglobin-based oxygen carrier to increase oxygen delivery was limited by its vasoactivity. In another prospective, randomised trial,[81]

Panel 3: **Current artificial oxygen carriers in clinical trials**

Compound	Attributes
Perflubron (perfluorooctyl bromide), Oxygent, Alliance Pharmaceuticals, San Diego, CA	60% emulsion of perfluorocarbon has now completed one phase 3 evaluation in Europe,[83] USA, and Canada. Due to unexplained results possibly related to clinical trial design flaws, the cardiac and non-cardiac transfusion avoidance studies in the USA were terminated early in 2001
DCLHB-HemAssist, Baxter Healthcare, Roundtree, IL	Negative outcomes in phase 2 and clinical trials caused research to be terminated in 1999
Glutaraldehyde polymerised bovine haemoglobin, Hemopure, Biopure Corp, Boston, MA	Hemopure has a long storage capability at room temperature. Oxygen delivery is three times greater then allogeneic blood because of better oxygen affinity. Applications include trauma and military settings along with surgical and acute needs
Polyoxyethylene glycol conjugated bovine haemoglobin, Enzon, Piscataway, NJ	Due to long half-life, administration once a week makes tumours more radiosensitive
Raffinose crosslinked and polymerised human haemoglobin HemoLink, Hemosol, Toronto, Canada	Controlled clinical trials in cardiac surgery have shown reduced exposure to allogeneic transfusion with few side-effects and no negative effect on mortality
Pyridoxylated and glutaraldehyde polymerised human haemoglobin, PolyHeme, Northfield Laboratories, Chicago, IL	Closest to human blood properties, Polyheme can be administered in large quantities (up to 5000 mL). This product is intended to be used in trauma patients. Clinical vasoconstriction has not been reported
Recombinant human haemoglobin- Optro, Somatogen, Boulder, CO, Baxter Healthcare, Roundtree, IL	Early problems with oxygen yield and production were observed. Purification was also a problem with *Escherichia coli*, but now is not. Further work on improving oxygen yield is underway with additional recombinants
Polynitroxylated polymerised haemoglobin, PNH, SynZyme Technologies, Irvine, CA	Haemoglobin-based oxygen carriers crosslinked with Dextran is associated with a right shift of oxydissociation and nitroxylation resulting in vasodilatation. This haemoglobin-based oxygen carrier has anti-inflammatory properties intended for cardiac surgery and trauma

more trauma patients died than controls, resulting in discontinuation of further product development from the manufacturer.

Perfluorocarbon emulsions can dissolve large amounts of any gas, including oxygen and carbon dioxide. These emulsions are effective for delivery of oxygen during haemodilution in patients undergoing orthopaedic surgery at 0·9 and at 1·8 g/kg perfluorocarbon doses.[82] In a multinational randomised study[83] of a perfluorocarbon solution to augment acute normovolaemic haemodilution during orthopaedic surgery, perfluorocarbon combined with 100% oxygen was more effective than autologous blood in reversal of physiological transfusion triggers. Because of the small sample size, efficacy of the perfluorocarbon solution in elimination of allogeneic blood exposure was not recorded. With their high affinity to dissolve gases, prevention of, and therapy for micro-embolic bubbles from cardiopulmonary bypass or preservation of solid organs for transplantation are other possible and desirable applications for which perfluorocarbons seem to be ideally suited.[84–86]

The two principal applications for the artificial oxygen carriers under clinical investigation are in patients with trauma[87] and in those who are undergoing surgery, with or without acute normovolaemic haemodilution. The rationale for use of artificial oxygen carriers with haemodilution is three-fold: the cellular haemoglobin collected during haemodilution would be used to replace the haemoglobin solution or other synthetic oxygen carrier as it is eliminated; use of artificial oxygen carriers would permit more aggressive haemodilution with lower targeted cellular haemoglobin concentrations than would otherwise be tolerated; and an artificial oxygen carrier could serve as a replacement fluid during blood loss.[88]

At present, artificial oxygen carrier products are in various stages of clinical development (panel 3). If approved by the FDA, they would most likely be readily applied in military casualties and in trauma patients, massive surgical blood loss settings, or in fulminant haemolytic anaemias.[89] The role of these substances in these and other arenas will most likely be determined by issues related to blood inventory and costs, rather than the safety of the blood supply.

Other beneficial molecules in human blood are being identified, isolated, and characterised, leading to the availability of blood-derived or ex-vivo synthesised therapeutic agents. One likely candidate molecule is the von Willebrand factor-cleaving metalloprotease, which has been associated with thrombotic thrombocytopenic purpura. Treatment for this potentially fatal disorder requires daily plasma apheresis (typically for 1–2 weeks or longer) with plasma replacement.[90] During a therapeutic course, patients are generally exposed to over 200 blood donors.[91] In Canada, 39% of all plasma apheresis procedures are for treatment of thrombotic thrombocytopenic purpura.[92] In many patients with non-familial, idiopathic thrombotic thrombocytopenic purpura, activity of the von Willebrand factor-cleaving metalloprotease is reduced (typically as a result of an inhibitor), and the rarer familial recurrent thrombotic thrombocytopenic purpura is a result of gene mutations yielding a dysfunctional metalloprotease.[93–95] The actual protease has been isolated and partly sequenced.[96–98] Availability of a metalloprotease preparation might obviate the need for plasma apheresis and improve outcomes in this serious disorder.

Oversight

Whether transfusion services will participate in implementation or distribution of emerging bio-technologies (panel 1) such as pathogen inactivation and artificial oxygen carriers is not yet established. As both regulated and marketed pharmaceuticals, artificial oxygen carriers might be applied clinically as more traditional pharmaceutical therapeutics, similar to factor concentrates.

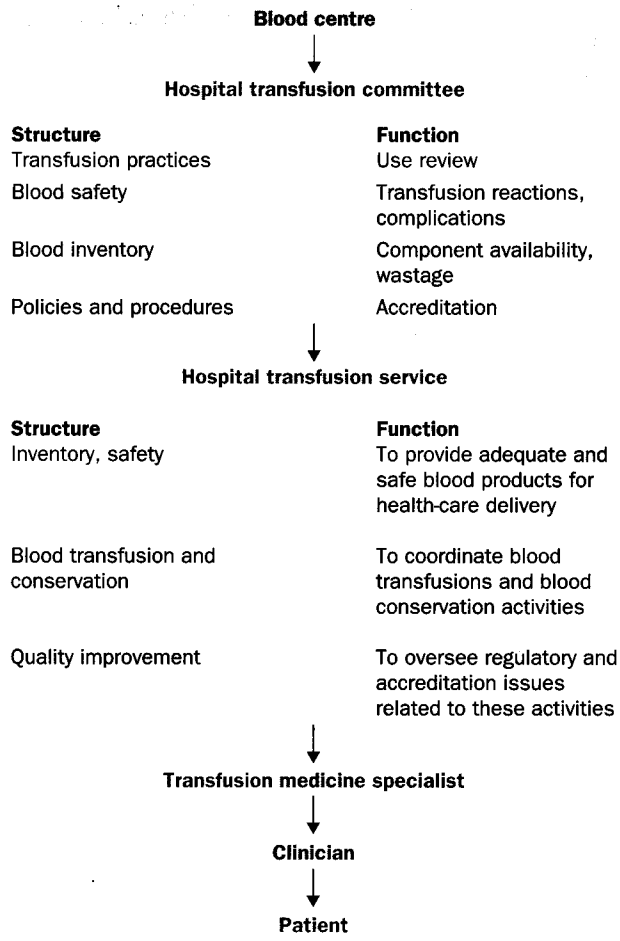

Figure 2: **Flow of blood components from "vein to vein"**
The physiology of the transfusion committee and the transfusion service helps define the job description of the transfusion medicine specialist, whose position between the transfusion service and the clinician emphasises the clinical role as consultant. Reprinted from reference 99, with permission from the publisher.

It is important that oversight of these biotechnology products and other specialised blood products (such as solvent detergent plasma, leukoreduced blood products, irradiated blood components, and cytomegalovirus negative blood components) be placed under the auspices of standing hospital medical committees such as a transfusion medicine committee, a pharmacotherapeutics committee, a surgical operating room committee, or a critical care committee (figure 2).[99] This process would mean that longitudinal reviews could be done about use of these agents, not only to assist in proper selection of patients, but also to establish efficacy, track serious adverse events, and assess costs. The promotion of such products by the commercial sector directly to consumers could undermine both institutional oversight and an evidence-based rationale for use.

Global perspective

Worldwide, over 75 million units of blood are estimated to be donated every year. In the USA, the yearly transfusion of 12·5 million units (M Sullivan, National Blood Data

Resource Center, personal communication) corresponds to transfusion of one blood unit every 0·39 s. Only 43% of WHO's 191 member states test blood for HIV, and hepatitis C and hepatitis B viruses. At least 13 million units of blood donated every year are not tested for these transmissible viruses. 80% of the world's population is estimated to have access to only 20% of the worldwide supply of safe blood. Every year, unsafe transfusion and injection practices are estimated to account for 8–16 million hepatitis B infections, 2·3–4·7 million hepatitis C infections, and 80 000–160 000 HIV infections.[100,101]

In the poorest countries, access to safe blood is financially prohibitive, since testing costs between US$40 and $50 per blood donation. Testing might also not be reliable, especially if done by inadequately trained staff or with inadequate equipment. Transmissible diseases are not the only issue, since many countries do not have an organised transfusion system and donated blood is simply unavailable.

Although safe and available blood is demanded and expected in developed countries, limitations in resources make this goal unattainable for poor developing countries. The British philosopher John Stuart Mill (1806–73) stated that "actions are right to the degree that they tend to promote the greatest good for the greatest number." Although our continued efforts to increase the safety of blood in developed countries are both impressive and commendable, more fundamental problems in developing countries need to be addressed.

Conflict of interest statement

Within the past 3 years, L T Goodnough has been a consultant for Ortho Biotech, Amgen, Novonordisk, and Hemosol; A Shander has been a consultant for Ortho Biotech, Amgen, Novonordisk, Abbott, Astra Zeneca, Alliance Pharmaceuticals, and Hemosol; and M E Brecher has been a consultant for BioMérieux (formerly Organon Teknika), Pall Biomedical, Mosaic Technologies, and Hemosol. M E Brecher has received research support from BioMérieux and Haemonetics and honoraria from BioMerieux, Pall Biomedical, and Mosaic Technologies.

References

1 Schmidt PJ. Blood and disaster: supply and demand. *N Engl J Med* 2002; **346:** 617–20.

2 Klein HG. Earthquake in America. *Transfusion* 2001; **41:** 1179–80.

3 Chapman J.Monitoring the capacity of the blood supply to meet demand. Presentation at the HHS Advisory Committee on Blood Safety and Availability. What lessons can be learned from the events of Sept 11, 2001, that would strengthen the safety and availability of the US blood supply? Transcript of 16th meeting. Vol I, Jan 31, 2002. http://www.hhs.gov/bloodsafety/transcripts/20020131.html (accessed Jan 5, 2002).

4 Nightingale S. The federal government role in assuring blood safety and availability during a disaster. Presentation at the HHS Advisory Committee on Blood Safety and Availability. What lessons can be learned from the events of Sept 11, 2001, that would strengthen the safety and availability of the US blood supply? Transcript of 16th meeting. Vol I, Jan 31, 2002. http://www.hhs.gov/bloodsafety /transcripts/20020131.html (accessed Jan 5, 2002).

5 Goodnough LT, Brecher ME, Kanter MH, Aubuchon JP. Transfusion medicine: part I. *N Engl J Med* 1999; **340:** 438–47.

6 Ouellette G.The experience and actions of the Washington, DC, blood community on and after September 11. Presentation at the HHS Advisory Committee on Blood Safety and Availability. What lessons can be learned from the events of Sept 11, 2001, that would strengthen the safety and availability of the US blood supply? Transcript of 16th meeting. Vol I, Jan 31, 2002. http://www.hhs.gov/bloodsafety/transcripts/20020131.html (accessed Jan 5, 2002).

7 Gilcher R. Lessons from previous disasters. Presentation at the HHS Advisory Committee on Blood Safety and Availability. What lessons can be learned from the events of Sept 11, 2001, that would strengthen the safety and availability of the US blood supply? Transcript of 16th meeting. Vol I. Jan 31, 2002. http://www.hhs.gov/bloodsafety/transcripts/20020131.html (accessed Jan 5, 2002).

8 Valeri CR, Ragno G, Pivacek LE, et al. A multicenter study of in vitro and in vivo values in human RBCs frozen with 40-percent (wt/vol) glycerol and stored after deglycerolization for 15 days at 4 degrees C in AS-3: assessment of RBC processing in the ACP 215. *Transfusion* 2001; **41:** 933.

9 Snyder E Blood community perspective on assuring blood safety and availability during a disaster. Presentation at the HHS Advisory Committee on Blood Safety and Availability. What lessons can be learned from the events of Sept 11, 2001, that would strengthen the safety and availability of the US blood supply? Transcript of 16th meeting. Vol I. Jan 31, 2002. http://www.hhs.gov/bloodsafety /transcripts/20020131.html (accessed Jan 5, 2002).

10 Kleinman SH, Glynn SA. Busch MP, Wright OJ, McMullen Q, Schreiber GB. Declining incidence rates and risks of transfusion-transmitted viral infections in US blood donors. *Vox Sang* 2002; **83:** 106.

11 Aubuchon JP, Birkmeyer JD, Busch MP. Safety of the blood supply in the United States: opportunities and controversies. *Ann Intern Med* 1997; **127:** 904–09.

12 CBS News. HIV-tainted blood infects two in Florida. http://www.cbsnews.com/stories/2002/07/19/health/main515694.shtml (accessed Dec 6, 2002).

13 da Silva Cardoso M, Koerner K, Kubanek B. The first case of HCV seroconversion after 3 years of HCV NAT screening in Baden-Wurttemberg. *Transfusion* 2000; **40:** 1422–23.

14 Yomtovian R, Lazarus HM, Goodnough LT, et al. A prospective microbiologic surveillance program to detect and prevent the transfusion of bacterially contaminated platelets. *Transfusion* 1993; **33:** 902–09.

15 Dyskstra A, Jacobs J, Yomtovian R. Prospective microbiological surveillance (PMS) of random donor (RDP) and single donor apheresis platelets (SDP). *Transfusion* 1998; **38** (suppl)**:** S104.

16 Leiby DA, Kerr KL, Campos JM, et al. A retrospective analysis of microbial contaminants in outdated random-donor platelets from multiple sites. *Transfusion* 1997; **37:** 259–63.

17 Goldman M, Blajchman MA. Blood product-associated bacterial sepsis. *Transfus Med Rev* 1991; **5:** 73–83.

18 Association Bulletin No 96-6. Bacterial contamination of blood components. AABB Faxnet, No 294, August, 1996. American Association of Blood Banks.

19 Jacobs MR, Palavecino E, Yomtovian R. Don't bug me: the problem of bacterial contamination of blood components-challenges and solutions. *Transfusion* 2001; **41:** 1331–34.

20 Ness PM, Braine HG, King K, et al. Single donor platelets reduce the risk of septic transfusion reactions. *Transfusion* 2001; **41:** 857–61.

21 Ollgaard M, Albjerg I, Georgen J. Monitoring of bacterial growth in platelet concentrates—one year's experience with the BactAlertTM System. *Vox Sang* 1998; **74** (suppl)**:** 1126.

22 Laan E, Tros C. Improved safety and extended shelf-life of leuco-depleted platelet concentrates by automated bacterial screening. *Transfusion* 1999; **39** (suppl)**:** 5S.

23 Vuetic D, Taseki J, Balint B, Mirovic V. The use of BacTAlert system for bacterial screening in platelet concentrates. *Vox Sang* 2000; **78** (suppl)**:** P371.

24 McDonald CP, Roy A, Lowe P, et al. The first experience in the United Kingdom of the bacteriological screening of platelets to increase shelf life to 7 days. *Vox Sang* 2000; **78** (suppl)**:** P375.

25 Brecher ME, Means N, Jere CS, et al. Evaluation of the BacT/ALERT 3D microbial detection system for platelet bacterial contamination: an analysis of 15 contaminating organisms. *Transfusion* 2001; **41:** 477–82.

26 AuBuchon JP, Cooper LK, Leach MF, et al. Bacterial culture of platelet units and extension of storage to 7 days. *Transfusion* 2001; **41** (suppl)**:** S1.

27 Brecher ME, Holland PV, Pineda A, et al. Bacterial growth in inoculated platelets: Implications for bacterial detection and the extension of platelet storage. *Transfusion* 2000; **40:** 1308–12.

28 Lin L, Cook DN, Wiesehahn GP, et al. Photochemical inactivation of viruses and bacteria in platelet concentrates by use of a novel psoralen and long-wavelength ultraviolet light. *Transfusion* 1997; **37:** 423–35.

29 Knutson F, Alfonso R, Dupuis K, et al. Photochemical inactivation of bacteria and HIV in buffy-coat-derived platelet concentrates under conditions that preserve in vitro platelet function. *Vox Sang* 2000; **78:** 209–16.

30 Corash L, Behrman B, Rheinschmidt M, et al. Post-transfusion viability and tolerability of photochemically treated platelet concentrates. *Blood* 1997; **90:** 267a.

31 McCullough J, Vesole D, Benjamin RJ, et al. Pathogen-inactivated platelets using Helinx technology are hemostatically effective in the thrombocytopenia patient. *Blood* 2001; **98:** 45a.

32 Nahlen BL, Lobel HO, Cannon SE, Campbell CC. Reassessment of blood donor selection criteria for United States travelers to malarious areas. *Transfusion* 1991; **31:** 786–88.

33 Guerrero IC, Weneger BG, Schultz MG. Transfusion malaria in the United States, 1972–1981. *Ann Intern Med* 1983; **99:** 221.

34 Mungai M, Tegtmeier G, Chamberland M, Parise M. Transfusion-transmitted malaria in the United States from 1963 through 1999. *N Engl J Med* 2001; **344:** 1973–78.

35 Schmunis GA. *Trypanosomo cruzi*, the etiologic agent of Chagas' disease: status in the blood supply in endemic and non-endemic countries. *Transfusion* 1991; **31:** 547–57.

36 Schmunis GA, Zueker F, Cruz JR, Cuchi P. Safety of blood supply for infectious disease in Latin American countries. *Am J Trop Med Hyg* 2001; **65:** 924–30.

37 Shulman IA, Appelman S, Saxena S, Hiti AL, Kirchhoff LV. Specific antibodies to *Trypansoma cruzi* among blood donors in Los Angeles, California. *Transfusion* 1997; **37:** 727–31.

38 Cimo PL, Luper WE, Scouroso MA. Transfusion-associated Chagas' disease in Texas: report of a case. *Tex Med J* 1993; **89:** 48–50.

39 Centers for Disease Control and Prevention. Chagas disease after organ transplantation–United States, 2001. *JAMA* 2002; **287:** 1795–96.

40 McQuiston JH, Childs JE, Chamberland ME, Tabor E. Transmission of tick-borne agents of disease by blood transfusion: a review of known and potential risks in the United States. *Transfusion* 2000; **40:** 274–84.

41 Brown P, Preece MA, Will RG. Friendly fire in medicine: hormones, homografts, and Creutzfeldt-Jacob disease. *Lancet* 1992; **340:** 24–27.

42 Dodd RY, Sullivan MT. Creutzfeldt-Jacob disease and transfusion safety: tilting at icebergs? *Transfusion* 1998; **38:** 221–23.

43 FDA. Revised preventative measures to reduce the possible risk of transmission of CJD and vCJD by blood and blood products. http://www.fda.gov/cber/gdlins/cjdvcjd.htm (acccessed Jan 8, 2002).

44 Consultant Pathologists Group Committee. Blood transfusion accidents. *BMJ* 1953; **2:** 390–91.

45 Linden JV, Wagner K. Voytovich AE, Sheehan J. Transfusion errors in New York State: an analysis of 10 years' experience. *Transfusion* 2001; **40:** 1207–13.

46 Williamson LM, Lowe S, Love E, et al. Serious hazards of transfusion. Initiative: analysis of first two annual reports. *BMJ* 1999; **319:** 16–19.

47 Sazama K. Reports of 355 transfusion-associated deaths: 1976 through 1985. *Transfusion* 1990; **30:** 583–90.

48 Goldman M, Remy-Prince S, Trepanier A, Decary F. Autologous donation error rates in Canada. *Transfusion* 1997; **37:** 523–27.

49 American Association of Blood Bank. Non-infectious serious hazards of transfusion. Bethesda, MD: American Association of Blood Bank (Association bulletin 01–4), June 14, 2001.

50 Aubuchon JP, Lipton KS. Is it time for blood banking to take off? *Transfusion* 2001; **41:** 964–67.

51 Battles JB, Kaplan HS, Van Der Schaff TW, Shea CE. The attributes of medical event-reporting systems. Experience with a prototype medical event-reporting system for transfusion medicine. *Arch Pathol Lab Med* 1988; **122:** 231–38.

52 Callum JL, Kaplan HS, Merkley LL, et al. Reporting of near-miss events for transfusion medicine: improving transfusion safety. *Transfusion* 2001; **41:** 1204–11.

53 Wenz B, Burns ER. Improvement in blood safety using a new blood unit and patient identification system as part of safe transfusion practice. *Transfusion* 1991; **31:** 401–03.

54 Jenson NJ, Crosson JT. An automated system for bedside verification of the match between patient identification and blood group identification. *Transfusion* 1996; **36:** 216–21.

55 Goodnough LT, Brecher ME, Kanter MH, Aubuchon JP. Transfusion Medicine. Part I. *N Engl J Med* 1999; **340:** 438–47.

56 Besarab A, Bolton WK, Browne JK, et al. The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. *N Engl J Med* 1998; **339:** 584–90.

57 Foley RN, Parfrey PS, Harnett JD, Kent GM, Murray OC, Barre PC. The impact of anemia on cardiomyopathy, morbidity, and mortality in end state renal disease. *Am J Kidney Dis* 1996; **28:** 53–61.

58 Canella G, LaCamma G, Sandrini M, et al. Reversal of left ventricular hypertrophy following recombinant human erythropoietin treatment of anaemic dialysed uraemic patients. *Nephrol Dial Transplant* 1991; **6:** 31–37.

59 Collins A, Ma JZ, Ebben J, et al. Impact of hematocrit on morbidity and mortality. *Semin Nephrol* 2000; **20:** 345–49.

60 Ma J, Ebben J, Xia H, et al. Hct level and associated mortality in hemodialysis patients. *J Am Soc Neph* 1999; **10:** 610–19.

61 Collins A, Xia H, Ebben J, et al. Change in Hct and risk of mortality. *J Am Soc Nephrol* 1998; **9:** 204A.

62 Collins AJ, Li S, St Peter W, et al. Death, hospitalization, and economic associations among incident hemodialysis patients with hematocrit values of 36 to 39%. *J Am Soc Nephrol* 2001; **12:** 2465–73.

63 National Kidney Foundation. K/DOQI. Clinical practice guidelines for the treatment of anemia of chronic kidney disease. *Am J Kidney Dis* 1997; **30:** S192–237.

64 Carson JL, Duff A, Poses RM, et al. Effect of anemia and cardiovascular disease on surgical mortality and morbidity. *Lancet* 1996; **348:** 1055–60.

65 Hebert PC, Wells G, Sweedale M, et al. Does transfusion practice affect mortality in critically ill patients? *Crit Care Med* 1997; **155:** 1618–23.

66 Silverberg OS, Wexler D, Sheps D, et al. The effect of correction of mild anemia in severe, resistant congestive heart failure using subcutaneous erythropoietin and intravenous iron: a randomized controlled study. *J Am Coll Cardiol* 2001; **37:** 1776–79.

67 Wu WC, Rathmore SS, Wang Y, Radford MJ, Krumholz HM. Effectiveness of blood transfusion in elderly patients with acute myocardial infarction. *N Engl J Med* 2001, **345:** 1230–36.

68 Goodnough LT, Bach RG. Anemia, transfusion, and mortality. *N Engl J Med* 2001; **345:** 1272–73.

69 Lenfant C. Transfusion should be monitored for undertransfusion as well as overtransfusion. *Transfusion* 1992; **32:** 873–74.

70 Sazama K. Is undertransfusion occurring? *Transfusion* 2001; **41:** 577–78.

71 National Heart, Lung, and Blood Institute. http://grants.nih.gov/grants/guide/rfa-files/rfa-HL-02-001.html (accessed Jan 2, 2002).

72 Goodnough LT, Brecher ME, AuBuchon JP. Transfusion Medicine. Part II. Blood Conservation. *N Engl J Med* 1999; **340:** 525–33.

73 Hedner U, Erhardtsen E. Potential role for recombinant factor VIIa in transfusion medicine. *Transfusion* 2002; **42:** 114–24.

74 Winslow RM. Blood substitutes—a moving target. *Nat Med* 1995; **1:** 1212–15.

75 Stowell CP, Levin J, Spiess BD, Winslow RM. Progress in the development of RBC substitutes. *Transfusion* 2001; **41:** 287–99.

76 Ma Z, Monk TG, Goodnough LT, et al. Effect of hemoglobin- and perflubron-based oxygen carriers on common clinical laboratory tests. *Clin Chem* 1997; **43:** 1732–37.

77 Scott MG, Kucik DF, Goodnough LT, Monk TG. Blood substitutes: evolution and future applications. *Clin Chem* 1997; **43:** 1724–31.

78 Rioux F, Drapeau G, Marceau F. Recombinant human hemoglobin selectively inhibits vasorelaxation elicited by nitric oxide donors in rabbit isolated aortic rings. *J Cardiovasc Pharmacol* 1995; **25:** 587–94.

79 Winslow RM. Blood substitutes. *Curr Opin Hematol* 2002; **9:** 146–51.

80 Kasper SM, Grune F, Walter M, Amr N, Erasmi H, Buzello W. The effects of increased doses of bovine hemoglobin on hemodynamics and oxygen transport in patients undergoing preoperative hemodilution for elective abdominal aortic surgery. *Anesth Analg* 1998; **87:** 284–91.

81 Sloan EP, Koenigsberg M, Gens D, et al. Diaspirin cross-linked hemoglobin (DCL-Hgb) in the treatment of severe traumatic hemorrhagic shock. *JAMA* 1999; **282:** 1857–64.

82 Keipert PE. Use of Oxygent, a perfluorochemical-based oxygen carrier, as an alternative to intraoperative blood transfusion. *Artif Cells Blood Substit Immobil Biotechnol* 1995; **23:** 381–94.

83 Spahn DR, van Brempt R, Theilmeier G, et al. Perflubron emulsion delays blood transfusions in orthopedic surgery. *Anesthesiology* 1999; **91:** 1195–208.

84 Jones JA. Red blood cell substitutes: current status. *Br J Anaesth* 1995; **74:** 697.

85 Maguire PJ. Stevens C, Humes HD, Shander A, Halpern NA, Pastores SM. Bioartificial organ support for hepatic, renal, and hematologic failure. *Crit Care Clin* 2000; **16:** 681–84.

86 Spahn DR, Leone BJ, Reves JG, Pasch T. Cardiovascular and coronary physiology of acute isovolemic hemodilution: a review of nonoxygen-carrying and oxygen-carrying solutions. *Anesth Analg* 1994; **78:** 1000–21.

87 Cothren C, Moore EE, Offner PJ, Haenel JB, Johnson JL. Blood substitute and erythropoietin therapy in a severely injured Jehovah's Witness. *N Engl J Med* 2002; **346:** 1097–98.

88 Brecher ME, Goodnough LT, Monk T. The value of oxygen-carrying solutions in the operative setting, as determined by mathematical modeling. *Transfusion* 1999; **39:** 396–402.

89 Mullon J, Giacoppe G, Clagett C, McCurie D, Dillard T. Transfusions of polymerized bovine hemoglobin in a patient with severe autoimmune hemolytic anemia. *N Engl J Med* 2000; **342:** 1638–43.

90 Bandarenko N, Brecher ME. United States thrombotic thrombocytopenic purpura apheresis study group: multicenter survey and retrospective analysis of current efficacy of therapeutic plasma exchange. *J Clin Apheresis* 1998; **13:** 133–41.

91 Bell WR, Braine HG, Ness PM, Kickler TS. Improved survival in thrombotic thrombocytopenic purpura-hemolytic uremic syndrome: clinical experience in 108 patients. *N Engl J Med* 1991; **325:** 398–403.

92 Clark WF, Rock GA, Buskard N, et al. Therapeutic plasma exchange:

an update from the Canadian Apheresis Group. *Ann Intern Med* 1999; **131:** 453–62.
93 Furlan M, Robles R, Galbusera M, et al. von Willebrand factor-cleaving protease in thrombotic thrombocytopenic purpura and the hemolytic-uremic syndrome. *N Engl J Med* 1998; **339:** 1578–84.
94 Tsai HM, Lian EC. Antibodies to von Willebrand factor-cleaving protease in acute thrombotic thrombocytopenic purpura. *N Engl J Med* 1998; **339:** 1585–89.
95 Levy GG, Nichols WC, Lian EC, et al. Mutations in a member of the ADAMTS gene family cause thrombotic thrombocytopenic purpura. *Nature* 2001; **413:** 488–94.
96 Fujikawa K, Suzuki H, McMullen B, Chung D. Purification of human von Willebrand factor-cleaving protease and its identification as a new member of the metalloproteinase family. *Blood* 2001; **98:** 1662–66.
97 Gerritsen HE, Robles R, Lammle B, Furlan M. Partial amino acid sequence of purified von Willebrand factor-cleaving protease. *Blood* 2001; **98:** 1654–61.
98 Zheng X, Chung D, Takayama TK, Majerus EM, Sadler JE, Fujikawa K. Structure of von Willebrand factor-cleaving protease (ADAMTS13), a metalloprotease involved in thrombotic thrombocytopenic purpura. *J Biol Chem* 2001; **276:** 41059–63.
99 Goodnough LT. What is a transfusion medicine specialist? *Transfusion* 1999; **39:** 1031–33.
100 Noel L. Safe blood starts with me, blood saves lives. Transcripts of World Health Day 2000, April 7, 2000.http://www.who.int/multimedia/whd2000/#noel (accessed Jan 5, 2002).
101 C Health. Millions need access to safe blood, says UN. http://www.canoe.ca/Health0004/07 blood.html (accessed Jan 5, 2002).