Miller Blood Transfusion

Blood transfusion

TABLE 46–1. American College of Surgeons Classes of Acute Hemorrhage

FACTORS	I /	II / III / IV
Blood loss,ml		
<=750 / 750–1,500 /1,500–2,000 /2,000 or more		
Blood loss, %BV		
>=15 / 15–30 / 30–40 / 40 or more		
Pulse, *bpm*		
>100 / >100 / >120 / 140 or higher		
Blood pressure		
Normal / Normal /Decreased / Decreased		
Pulse pressure (mm Hg)		
Normal/increased // Decreased //Decreased /Decreased		
Capillary refill test		
Normal /Positive /Positive /Positive		
Respirations *per minute*		
14–20 / 20–30 / 30–40 / >35		
Urine output, *mL/h*		
30 /20–30 /5–10 /Negligible		
CNS (mental status)		
Slightly anxious / Mildly anxious /Anxious, confused / Confused, lethargic		
Fluid replacement (3:1 rule)		
Crystalloid / Crystalloid / Crystalloid + blood / Crystalloid + blood		

Compatibility Testing

The ABO-Rh type, crossmatch, and antibody screen are frequently referred to as *compatibility tests.* These tests were designed to demonstrate harmful antigen-antibody interactions *in vitro* so that harmful *in vivo* antigen-antibody interactions could be prevented. Donor blood used for emergency transfusion of group-specific blood must be screened for hemolytic anti-A and/or anti-B antibodies. Also, all donor blood must be tested for the correct ABO and Rh type and screened for unexpected antibodies. Similarly, recipient blood must also undergo ABO-Rh typing, as well as testing for unexpected antibodies. Once this has been completed, proper selection of donor blood requires a test for compatibility between recipient blood and donor blood; this test is known as a crossmatch (Fig. 46–1).
FIGURE 46–1 Outline of the tests used for a crossmatch. The X over the word *crossmatch* means that the crossmatch is not included in the type and screen.

ABO-Rh Typing

Determination of the patient‘s correct blood type is exceedingly important because the most serious and tragic reactions are usually caused by accidental transfusion of ABO-incompatible blood. These reactions are due to naturally occurring antibodies (anti-A and anti-B), which activate, complement, and lead to rapid intravenous hemolysis. Anti-A and/or anti-B antibodies are formed whenever the individual lacks either or both of the A and B antigens. In essence, antibodies are directed against those antigens that are lacking in the individual‘s own cells. ABO typing is performed by testing RBCs for the A and B antigens and the serum for the A and B antibodies before transfusion (Table 46–2).

TABLE 46–2. ABO Compatibility Testing

The only additional required testing is that for the Rh(D) antigen. Antigen D is a very common one and, except for the A and B antigens, the one most likely to produce immunization. Approximately 60 to 70 percent of Rh(D)-negative recipients are immunized (produce anti-D) if they are given blood transfusions with Rh(D)-positive blood. About 85 percent of individuals possess the D antigen and are termed Rh(D)-positive; the remaining 15 percent, who lack the D antigen, are termed Rh(D)-negative. Because

anesthesiologists and surgeons often have difficulty understanding the blood grouping system, is included to facilitate identification of donor blood groups whose blood patients can receive.

Crossmatching

A crossmatch is essentially a trial transfusion within a test tube in which donor RBCs are mixed with recipient serum to detect a potential for serious transfusion reaction. The crossmatch can be completed in approximately 45 to 60 minutes and is carried out in three phrases: an immediate phase, an incubation phase, and an antiglobulin phase.

The first phase is conducted at room temperature and is a check against errors in ABO typing. It detects ABO incompatibilities and those caused by naturally occurring antibodies in the MN, P, and Lewis systems. This takes approximately 1 to 5 minutes to complete.

The second phase involves incubation of the first-phase reactions at 37°C in albumin or low-ionic strength salt solution. The addition of albumin and low-ionic-strength salt solution aids in the detection of incomplete antibodies or those antibodies that are able to attach to a specific antigen (sensitization) but are unable to cause agglutination in a saline suspension of RBCs. This phase primarily detects antibodies in the Rh system. The incubation of 30 to 45 minutes in albumin and of 10 to 20 minutes in low-ionic-strength salt solution in this phase is of sufficient duration to allow antibody uptake sensitization by cells so that incomplete antibodies missed in this phase can be detected in the subsequent antiglobulin phase.

The last, and third, phase of the crossmatch, the indirect antiglobulin test, involves the addition of antiglobulin sera to the incubated test tubes. With this addition, antihuman antibodies present in the sera become attached to the antibody globulin on the RBCs, thus causing agglutination. This antiglobulin phase detects most incomplete antibodies in the blood group systems, including the Rh, Kell, Kidd, and Duffy blood group systems.

Although all three phases of the crossmatch are important, the first two stages are of prime importance in preventing serious hemolytic transfusion reactions (see Type and Screen). The incubation and antiglobulin phases are especially important because the antibodies appearing in these phases are capable of causing serious hemolytic reactions. Except for hemolytic reactions involving anti-A and anti-B, reactions caused by antibodies appearing in the immediate phase (RT) are frequently less severe. This is because many of the antibodies appearing in this phase are naturally occurring antibodies present in a low titer and are not reactive at physiologic temperatures.

Antibody Screening

The antibody screen is also carried out in three phases and is similar in length to the crossmatch. The screen, however, is a trial transfusion between the recipient serum and commercially supplied RBCs that are specifically selected to contain optimal numbers of RBC antigens, or those antigens that will react with antibodies that are commonly implicated in hemolytic transfusion reactions.

The screen for unexpected antibodies is also used on donor serum and is performed shortly after withdrawal of blood from the donor. It is necessary to screen donor serum for unexpected antibodies in order to prevent their introduction into the recipient serum. This screen is performed primarily to prevent reactions between transfused donor units.

Approaches Requiring Less Than a Complete Crossmatch

Type and Screen

The term *type and screen* refers to elimination of the crossmatch in which blood is set aside with only the ABO-Rh type having been determined and antibody screening having been performed. The type and screen without crossmatch determines both the ABO-Rh of the patient and the presence of the most commonly found unexpected antibodies. Specifically, the patient‘s serum is screened for the presence of unexpected antibiotics by incubating it with selected reagent RBCs (screen cells). 28 These cells contain all antigens capable of inducing clinically significant RBC antibody reactions.

Complete transfusion testing for compatibility between donor and recipient blood ensures optimal safety and therapeutic effect of transfused blood. In some cases, however, the crossmatch is eliminated, and blood can be set aside in which only the ABO-Rh type and antibody screen are performed (type and screen). For those few patients in whom the antibody screen reveals the presence of unexpected antibody, the antibody is subsequently identified in the blood bank, and units of blood lacking the corresponding antigen are set aside for surgery. If an emergency transfusion is required after type and screen alone, an immediate-phase crossmatch is performed before transfusion to eliminate reactions that may result from human errors in ABO-Rh typing. Blood given in this manner is more than 99 percent effective in preventing incompatible transfusion reactions due to unexpected antibodies. 29 The type and screen without the complete crossmatch does not protect against reactions due to antibodies reactive against lower-incidence antigens, those not represented on the screening cells but present on the donor RBCs. Generally, antibodies that are not detected in the type and screen are weakly reactive antibodies that do not result in serious hemolytic transfusion reactions. In a study of 13,950 patients, Oberman et al 30 discovered only 8 "clinically significant" antibodies after complete crossmatch that were not detected during the antibody screening. The antibodies were all in lower titer and were believed by Oberman and coworkers to be unlikely to cause serious hemolytic reactions.

The type and screen should not be confused with the term *type and hold.* The latter term refers to a sample of blood from a potential blood recipient received by the blood bank in which the blood type but no crossmatch has been ordered. This term is misleading because it does not denote how long the blood should be held, nor does it indicate that an antibody screen has been performed on the sample. However, in most cases in which a type and hold has been ordered, an antibody screen is performed on that sample. Because of the confusion that has arisen with type and screen, the type and hold terminology and method of ordering blood have been abandoned by most blood banks.

Maximal Surgical Blood Order Schedule

Routine preoperative crossmatching of blood for surgical cases means that crossmatched blood is unavailable for others for 24 to 48 hours. During this time, 1 to 2 days is lost, and the chance for outdating increases. A second aspect relates to the growing realization that, for certain elective surgical procedures, the number of crossmatched units that are ordered frequently far exceeds the number actually transfused. To quantify this problem better, the crossmatch-to-transfusion (C/T) ratio has been used. If the C/T ratio is high, the blood bank is burdened with keeping a large blood inventory, using excessive personnel time, and having a high incidence of outdated units. Sarma 31 recommended that for surgical procedures in which the average number of units transfused per case is less than 0.5, determination of the ABO-Rh type and a screen of the patient serum for unexpected antibodies (type and screen) should be used. This would be in lieu of a complete type and crossmatch for patients with negative antibody screens. For those with a positive antibody screen, the blood bank must provide compatible units that lack the corresponding antigen. Blood banks attempt to maintain C/T ratios of 2.1 to 2.7. 31 To increase utilization rate and lower the C/T ratio, blood banks attempt to decrease the emphasis on crossmatching of blood through such means as the type and screen and such programs as the maximal surgical blood order schedule. 32 This schedule consists of a list of surgical procedures and the maximum number of units of blood that the blood bank will crossmatch for each procedure. This schedule is based on the blood transfusion experience for surgical cases in hospitals in which the schedule is employed. Each hospital's maximal surgical blood order schedule is developed by both the suppliers and the users of blood in that hospital, such as blood bankers, anesthesiologists, and surgeons.

Is the Crossmatch Really Needed?

In previously transfused or pregnant patients, only about 1 patient in 100 may have an irregular antibody other than the anti-A and/or anti-B antibodies. However, some of these irregular antibodies are reactive only at temperatures below 30°C and therefore are insignificant in most transfusions. Others that are reactive at about 30°C can produce serious reactions if the transfused cells contain appropriate antigen. In order of probable significance, anti-Rh(D), Kell, C, E, and Kidd are the most common of clinically significant antibodies. After anti-A and anti-B, anti-Rh(D) is the most common significant antibody. If the correct ABO and Rh blood type is given, the possibility of transfusing incompatible blood is less than 1 chance in 1,000. Put in other terms, ABO-Rh typing alone results in a 99.8 percent chance of a compatible transfusion, the addition of an antibody screen increases the safety to 99.94 percent, and a crossmatch increases this to 99.95 percent. 33

The blood bank can reduce the chance of incompatibility by performing an antibody screen. The chances of this screening test's missing an antibody that is potentially dangerous has been estimated to be no more than 1 in 10,000.

Emergency Transfusion

In many situations, there is urgent need for blood before completion of compatibility testing (ABO-Rh, antibody screen, and crossmatch) (Ch. 62). For those situations that do not allow time for complete testing, an abbreviated format for testing can be used. The preferred order for the selection of partially crossmatched blood is as follows.

Type-Specific Partially Crossmatched Blood

When using uncrossmatched blood, it is best to obtain at least an ABO-Rh typing and an immediate-phase crossmatch. This incomplete crossmatch is accomplished by adding the patient's serum to donor RBCs at room temperature, centrifuging it, and then reading it for macroscopic agglutination. This takes 1 to 5 minutes and eliminates serious hemolytic reactions resulting from errors that may occur in ABO typing. Only a few unexpected antibodies outside the ABO systems are detected, such as those directed against antigens in the MN, P, and Lewis systems, most of which are not clinically significant.

Type-Specific, Uncrossmatched Blood

For proper use of type-specific blood, the ABO-Rh type must be determined during the patient's hospitalization. Blood types from historical records, relatives, ambulance drivers, and other hospitals are frequently inaccurate. For those who have never been exposed to foreign RBCs, most ABO type-specific transfusions are successful. Caution should be used for those patients who have previously received transfusions or have had pregnancies. In the author's experience in the military, type-specific uncrossmatched blood was frequently used in emergencies with no serious consequence. In the civilian setting, using 1 year's experience with 56 patients, uncrossmatched, type-specific blood for emergency transfusion produced no adverse effects, even though complete serologic testing had not been performed.[34] These authors concluded that although the use of uncrossmatched blood is usually safe, the potential for serious reaction still exists, and they thus cautioned against its indiscriminate use. Specifically, about 1 in 1,000 patients has an unexpected antibody detected in crossmatch. For those who have previously been exposed to RBC antigens, transfusion of the ABO-Rh type-specific uncrossmatched blood may be more hazardous. For every 100 of these individuals, one has an antibody detected in the crossmatch.

Type O Rh-Negative (Universal Donor), Uncrossmatched Blood

Type O blood lacks both the A and B antigens and consequently cannot be hemolyzed by anti-A or anti-B antibodies in the recipient's blood (see Tables 46–2 and 46–3). Because of this, type O blood has been termed the *universal donor* and can be used in emergency transfusion when typing or crossmatching is not available. However, some type O donors produce high titers of hemolytic IgG, IgM, anti-A, and anti-B antibodies. High titers of these hemolysins in donor units are capable of causing destruction of A or B red blood cells of a non–type O recipient. Thus, type O Rhnegative uncrossmatched packed RBCs should be used in preference to type O Rh-negative whole blood because packed erythrocytes have smaller volumes of plasma and are almost free of hemolytic anti-A and anti-B antibodies. If type O Rh-negative whole blood is to be used, the blood bank must supply type O blood that is free of hemolytic anti-A and anti-B antibodies.

TABLE 46–2. ABO Compatibility Testing

TABLE 46–3. Donor Blood Groups That Patients Can Receive

During emergency transfusion of more than two units of type O Rh-negative uncrossmatched whole blood, the patient probably cannot be switched to his or her blood type (A, B, or AB) once the blood bank determines the correct blood type. Switching could cause major intravascular hemolysis of donor RBCs by increasing titers of transfused anti-A and anti-B. Continued use of O Rh-negative whole blood results only in minor hemolysis of recipient RBCs, with hyperbilirubinemia as the only complication. The patient must not be

transfused with his or her correct blood type until the blood bank determines that the transfused anti-A and anti-B has fallen to levels that permit safe transfusion of type-specific blood.

Specific Recommended Protocol

In view of the aforementioned considerations, the following steps are recommended in patients who are hypovolemic and require blood transfusion:

1.
Infuse crystalloids or colloids
2.
Draw a blood sample for typing and cross-matching
3.
If crossmatched blood is not ready to give: typespecific or type O Rh-negative cells, or type O Rh-positive cells for males or postmenopausal females without a history of transfusions; type-specific, partially crossmatched blood; type-specific, crossmatched blood

Storage of Blood

Citrate phosphate dextrose adenine (CPDA-1) is an anticoagulant preservative in which blood is stored at 1 to 6°C. Citrate is an anticoagulant, phosphate serves as a buffer, and dextrose is a red cell energy source. The addition of adenine to CPD solution allows RBCs to resynthesize adenosine triphosphate (ATP), which extends the storage time from 21 to 35 days. As a result, RBCs or whole blood can be stored for 35 days when stored in CPDA-1. 35 The shelf life can be extended to 42 days when AS-1 (Adsol) or AS-3 (Nutricel) is used. 36, 37 Adsol contains adenine, glucose, mannitol, and sodium chloride; Nutricel contains glucose, adenine, citrate, phosphate, and sodium chloride. This duration of storage has been set by U.S. federal regulation and is determined by the requirement that at least 70 percent of the transfused RBCs remain in circulation for 24 hours after infusion. RBCs that survive 24 hours after transfusion disappear from the circulation at a normal rate. Those that do not survive are subsequently removed from the circulation by the blood recipient.

The citrate ion prevents clotting by binding calcium; dextrose allows the RBCs to continue glycolysis and thus maintain sufficient concentrations of high-energy nucleotides (ATP) to ensure continued RBC metabolism and subsequent viability during storage. The storage at 1 to 6°C assists preservation by slowing the rate of glycolysis approximately 40 times the rate at body temperature. The addition of adenine prolongs storage time by increasing RBC survival by allowing RBCs to resynthesize the ATP needed to fuel metabolic reactions. Without adenine, RBCs gradually lose their ATP and their ability to survive after transfusion.

During storage of whole blood and packed RBCs, a series of biochemical reactions occur that alter the biochemical makeup of blood and account for some of the complications that are discussed later. During storage, RBCs metabolize glucose to lactate, hydrogen ions accumulate, and plasma pH decreases. The storage temperatures of 1 to 6°C stimulate the sodium-potassium pump, and RBCs lose potassium and gain sodium. The osmotic fragility of RBCs increases during storage, and some cells undergo lysis, resulting in elevated plasma hemoglobin levels. Also, storage is associated with progressive decreases in RBC concentrations of ATP and 2,3-diphosphoglycerate (2,3-DPG).

Interestingly packed RBCs have a slightly lower survival than whole blood (Table 46–4), although values for hemoglobin and potassium concentrations may appear somewhat high in 35-day stored RBC concentrates. However, it should be remembered that the total plasma volume in the concentrates is only 70 mL.

TABLE 46–4. Properties of Whole Blood and Packed Red Cell Concentrates Stored in CPDA-1

DAYS OF STORAGE
PARAMETER 0/ 35 (WHOLEBLOOD)
/ 35 (PACKED CELLS)

pH 7.55/ 6.73/ 6.71
Plasma hemoglobin (mg/dL)
0.50 /46 /246.0

Plasma potassium (mEq/L)
4.2 /17.2/ 76.0
Plasma sodium (mEq/L)
169 /153 / 122
Blood dextrose (mg/dL)
440 / 282 / 84
2,3-Diphosphoglycerate (?M/mL) 13.2 / <1 / <1
Percent survivala
— / 79 / 71

Frozen Storage

Satisfactory storage of RBCs in the frozen state became possible when these cells, mixed with glycerol, could be frozen and thawed without damage. RBCs previously frozen to 79°C in glycerol survive well in humans. RBCs must be free from glycerol before being transfused; unfortunately, a simple and inexpensive method of removing the glycerol has been difficult to develop. Valeri 38 studied the efficacy of using frozen RBCs and has attempted to simplify the method of freezing and thawing RBCs to make it a more viable process. The advantages of frozen and thawed RBCs are the following: (1) blood of rare types can be stored for long periods, increasing viability and eliminating outdating; (2) frozen, reconstituted blood is believed to be safer in patients who are especially susceptible to allergic reactions, because the freezing and washing process reduces sites with histocompatible antigens; (3) frozen washed blood may reduce risk of transfusion hepatitis; (4) frozen blood, low in fibrin and leukocytic aggregates, would be safer in patients requiring massive blood transfusion; and (5) frozen RBCs may be desirable in clinical conditions requiring prompt tissue oxygenation because normal levels of 2,3-DPG are retained in frozen erythrocytes. The efficacy of using frozen, thawed RBCs on a large-scale basis was proved possible at Cook County Hospital in Chicago, during a 28-month period. 39 In my opinion, there can be no doubt that blood can be stored for years, and this certainly would help alleviate the problem of having uncommon blood types not readily available. The incidence of transfusion reactions can clearly be reduced. Furthermore, the use of frozen RBCs can minimize alloimmunization to human leukocyte antigen and to membrane-specific antigens present on transfused white blood cells. However, these advantages can be more readily achieved by use of currently available washing devices. However, the original claim that the use of frozen RBCs would decrease the incidence of hepatitis seems to be unfounded. 40 As a result, frozen storage will continue to be used only on a limited basis.

Heparin

Whole blood stored in heparin is used in some situations for priming the pump during cardiopulmonary bypass. Heparinized whole blood is used by some clinicians in open-heart surgery to prevent cardiac abnormalities that might result from depression of ionized calcium levels by the citrate in other storage solutions. Furthermore, factor VIII complex is more stable than when other storage solutions are used for storage. Heparin anticoagulant is not a RBC preservative because it lacks glucose. Its anticoagulant effect is also neutralized during storage by the thromboplastic substances liberated by the cellular elements of blood during storage. Consequently, blood stored in heparin must be used within 24 to 48 hours of collection.

Complications

Changes in Oxygen Transport

RBCs are transfused primarily to increase transport of oxygen to tissues. An increase in the circulating red cell mass produces an increase in oxygen uptake in the lungs and a corresponding probable increase in oxygen delivery to tissues. The respiratory function of red cells may be impaired during preservation, making it difficult for them to release oxygen to the tissues immediately after transfusion.

In 1954, Valtis and Kennedy 41 first described a leftward shift of the oxygen dissociation curve *in vitro,* the magnitude of which was directly related to the length of time the acid citrate dextrose (ACD) blood had been stored. After transfusion of 7-day or older ACD blood, the oxygen dissociation curves of all patients also shifted to the left. The magnitude of the left shift was related to the volume and storage time of the infused ACD blood. In some cases, the curve remained shifted to the left for as long as 24 hours after transfusion.

Review of the Oxygen Dissociation Curve

The oxygen dissociation curve is determined by plotting the partial pressure of oxygen (PO2) in blood against the percentage of hemoglobin saturated with oxygen (Fig. 46–2). As hemoglobin becomes more saturated, the affinity of hemoglobin for oxygen also increases. This is reflected in the sigmoid shape of the curve, which indicates that a decrease in PaO2 makes considerably more oxygen available to the tissues. Thus, the sigmoid shape of the curve implies greater efficiency of blood transportation of oxygen from the lungs to tissues.
FIGURE 46–2 Factors that shift the oxygen dissociation curve. (From Miller178)

Shifts in the oxygen dissociation curve are quantitated by the P50, which, by convention, is the partial pressure of oxygen at which hemoglobin is half saturated with oxy-gen at 37°C and pH 7.4. A low P50 indicates a left shift in the oxygen-dissociation curve and an increased affinity of hemoglobin for oxygen; in other words, the left shift of the curve indicates that a lower-than-normal oxygen ten-sion saturates hemoglobin in the lung and the subsequent release of oxygen to the tissues occurs at a lower than normal capillary oxygen tension. An increased affinity may be enough to ensure that oxygen is released to the tissues unless the tissue PO2 is in the hypoxic range. The theoretical and clinical evidence supporting the accuracy of this hypothesis during infusion is discussed in the following sections.

Theoretical Evidence

A close relationship between the oxygen affinity of stored blood and intraerythrocytic 2,3-DPG has been established. 42 The intraerythrocytic 2,3-DPG levels decrease stored bank blood. Alkalosis and hypothermia shift the curve to the left even more (Fig. 46–2). Support for the importance of these shifts in the curve base can be derived from studies that manipulate the Fick equation, that is, that cardiac output (CO) equals oxygen consumption (O2) divided by the arteriovenous oxygen difference (CaO2 – CvO2, or C(a–v)O2). Rearranged, the equation reads

$$CvO2 = CaO2 – VO2 /CO$$

Therefore, mixed venous oxygen content or tension reflects the relationship between oxygen consumption and cardiac output. A low mixed-venous oxygen tension suggests that cardiac output cannot meet the tissue oxygen demands.

Clinical Evidence

The clinical evidence is not consistent, reflecting the difficulty of conducting a systematic study of seriously ill patients in varied clinical settings. Kopriva et al 43 found that 2,3-DPG levels decreased in 31 seriously injured battle casualties, each of whom received 12 or more units of ACD-stored blood. Furthermore, transfusion of fresh or stored blood did not influence the 2,3-DPG levels. The more common finding is that the P50 and 2,3-DPG levels do decrease after infusion of stored blood. 44 Although Sheldon 45 did find low P50 and 2,3-DPG values after infusion of CPD-stored blood (at 90% of the blood volume), no correlation between these values and cardiac index was found. On a theoretical basis, however, the left shift in the oxygen dissociation curve and the increased affinity for oxygen may increase cardiac output and work of the heart. 44 If a patient has marginal cardiac reserve and cannot increase cardiac output, tissue hypoxia may occur.

Although this evidence is suggestive, specific organ hypoxia has not been shown to result from infusion of blood with a low P50 or from increased affinity for oxygen. Valeri and Collins 46 performed a study in a group of patients who especially depended on adequate levels of 2,3-DPG for oxygen transport. Patients who had anemic hypoxia were transfused with three to five units of washed, liquid-stored RBCs that were depleted of 2,3-DPG and experienced an increased affinity for oxygen. No change in cardiac index or oxygen consumption resulted. Therefore, even in patients in whom 2,3-DPG is especially important for oxygen transport, no changes occurred. In fact, Bowen and Fleming 47 showed that although oxyhemoglobin affinity increases after transfusion of stored blood, arteriovenous oxygen extraction by organs or tissue may not be altered by changes in oxyhemoglobin affinity, particularly if a compensatory flow mechanism takes place at the capillary level. Such mechanisms may open capillaries, permitting increased blood flow to tissue, thereby increasing cardiac output and reducing the capillary tissue oxygen gradient to maintain the rate of tissue oxygen extraction. Because of the low P50 and the increased oxyhemoglobin

affinity of stored blood, assessment of specific organ function is necessary to substantiate the possible injurious effect of stored blood. Marik and Sibbard 9 found that the administration of blood that had been stored for more than 15 days actually decreased intramucosal pH, suggesting that splanchnic ischemia had occurred. Was this effect due to low 2,3-DPG levels in the stored blood and to an increased affinity of hemoglobin for oxygen? Despite these data, the evidence that possible changes in oxygen affinity from blood transfusions are important is not available. Therefore, it is difficult to come to definitive conclusions.

Coagulation

A bleeding tendency is often present in massively transfused patients. This coagulopathy is caused by a combination of factors of which the most important are the volume of blood given and the duration of hypotension or hypoperfusion. 48 Patients who are well perfused and are not hypotensive for a long period of time (e.g., 1 hour) can tolerate multiple units of blood without developing a coagulopathy. Clearly, the patient who is hypotensive and has received many units of blood probably has a coagulopathy from both disseminated intravascular coagulation (DIC) and dilution of coagulation factors from stored bank blood. When such bleeding occurs, the differential diagnosis for a patient who did not have a pretransfusion coagulopathy (e.g., hemophilia) is dilutional thrombocytopenia, low factors V and VIII, DIC, or hemolytic transfusion reaction. Clinical manifestations include oozing into the surgical field, hematuria, gingival bleeding, petechial bleeding from venipuncture sites, and ecchymoses.

Dilutional Thrombocytopenia

Dilutional thrombocytopenia is a cause of a hemorrhagic diathesis in a patient who has received multiple units of bank blood. At a storage temperature of 4°C, platelets in stored blood are damaged sufficiently to be readily trapped and absorbed by the reticuloendothelial system soon after infusion. Even those platelets that are not immediately stored have a reduced survival time. Considering survival time and viability, total platelet activity is only 50 to 70 percent of the original *in vivo* activity after 6 hours of storage in bank blood at 4°C. After 24 or 48 hours of storage, platelet activity is only about 10 or 5 percent of normal, respectively. Thus, infusion of bank blood stored for longer than 24 hours dilutes the available platelet pool. In one study during the Vietnam conflict, platelet counts were found to decrease to below 100,000/mm3 when 10 to 15 units of blood had been given to acutely wounded, previously healthy soldiers. 49 Obviously, the platelet count in smaller, older patients may decrease to 100,000/mm3 after fewer units of blood because these patients have a smaller blood volume and possibly a lower preoperative platelet count than soldiers. I strongly emphasize the importance of the platelet count because when it is approximately 75,000/mm3 or lower, a hemorrhagic diathesis is likely to occur (Table 46–5).

TABLE 46–5. Correlation Between Platelet Count and Incidence of Bleeding

Although major emphasis had been placed on monitoring the platelet count, several authors 48, 50, 51 have questioned the role of dilutional thrombocytopenia in the coagulopathy of massively transfused patients. They correctly point out that the platelet count rarely decreases as low as what would be predicted from dilution alone (Fig. 46–3). This is probably because platelets are released into the circulation from the spleen and bone marrow and because of the presence of nonfunctional platelets. Furthermore, Reed et al 51 found no benefit to prophylactic platelet administration during massive transfusion. Platelets should not be given to treat laboratory evidence of thrombocytopenia unless clinical coagulopathy is also present. Treating laboratory numbers without correlation with the clinical status is fundamentally contrary to good medical practice; transfusion medicine is no exception. Clearly, when the platelet count is below 50,000 to 75,000/mm3, a bleeding problem is likely and is probably a combination of dilutional thrombocytopenia and DIC. Platelet therapy would be appropriate in this situation (see Platelet Concentrates).
FIGURE 46–3 Mean platelet counts after massive transfusions in relation to number of units of blood transfused. Observed versus predicted values calculated on the basis of blood exchange model. (From Myllylä179)

To place such emphasis on the platelet count as a guide is appropriate, as defended previously, with some exceptions. For example, patients with chronic thrombocytopenia or leukemia are commonly known to survive and not have a hemorrhagic diathesis with a platelet count lower than 15,000 cells/mm3 . However, this does not negate the general guideline that patients with a platelet count of less than 75,000 cells/mm3 are likely to bleed. For unexplained reasons, patients with an acutely induced thrombocytopenia (e.g., from blood transfusions) develop a hemorrhagic diathesis at a much higher platelet count than do patients with a

chronically induced thrombocytopenia (e.g., idiopathic thrombocytopenia purpura). Furthermore, a higher platelet count is required to maintain adequate hemostasis with a surgical incision or trauma, because damaged capillaries require platelets to plug the holes. Thus, the platelet count is a reasonably accurate guide as to when patients will develop a bleeding problem from dilutional thrombocytopenia (see Table 46–5).

Low Factors V and VIII

Most of the factors are stable in stored blood, with two exceptions: factors V and VIII. 52 These factors gradually decrease to 15 and 50 percent of normal, respectively, after 21 days of storage. Furthermore, packed RBCs even have fewer coagulation factors. Consequently, administration of fresh frozen plasma (FFP), which contains all the factors except platelets, has been recommended on either a therapeutic or a prophylactic basis. However, this practice is of questionable benefit because only 5 to 20 percent of factor V and 30 percent of factor VIII are needed for adequate hemostasis during surgery. In other words, in spite of a patient‘s receiving massive blood transfusion, factors V and VIII rarely decrease below those levels required for hemostasis. Miller et al 49 examined this problem by giving 500 to 1,000 mL of FFP to five patients who had received more than 15 units of bank blood and who had a clinically significant hemorrhagic diathesis. Despite the partial thromboplastin times (which measure all factors except VII and XIII) and platelets‘ having returned to normal, bleeding persisted in every patient. Only when platelets in the form of fresh blood were administered did bleeding cease. 49 Thus, although low factors V and VIII appear to be an unlikely primary cause of bleeding during massive blood transfusion, such deficiencies may intensify bleeding from other causes, usually dilutional thrombocytopenia in the case of blood transfusion.

Despite evidence to the contrary, FFP continues to be commonly given for treatment of transfusion-induced coagulopathies. The overall increased use of FFP in the 1970s led the National Institutes of Health to conduct a consensus conference on this issue in 1985. 53 The conference concluded that there was little or no scientific evidence for the administration of FFP as part of the therapy for coagulopathy induced by multiple blood transfusion. Despite the National Institutes of Health statement, component blood therapy, especially FFP, continues to be given. 54 If the clinician insists on seriously considering giving FFP, the following criteria should be established:

1.
Generalized bleeding that cannot be controlled with surgical sutures or cautery
2.
Partial thromboplastin time at least 1.5 times normal
3.
Platelet count greater than 70,000/mm3 (to ensure that thrombocytopenia is not the cause of bleeding)

Disseminated Intravascular Coagulation

The coagulation system consists of clotting and fibrinolytic mechanisms. The function of the former is to prevent excessive blood loss, and that of the latter is to ensure circulation within the vasculature. With DIC, the clotting system is deranged, and this leads to disseminated fibrin deposition, which renders the fluid blood unclottable. The deposited fibrin may severely alter the microcirculation and lead to ischemic necrosis in various organs, particularly the kidney. The unclottable blood or circulating serum may induce a severe hemorrhagic diathesis.

The specific reasons for the development of DIC are usually not apparent. However, hypoxic acidotic tissues with stagnant blood flow probably release tissue thromboplastin either directly or through liberation of some toxin. In sepsis and eventual organ failure, the pathogenesis of DIC is more apparent. Apparently the extrinsic route of coagulation is activated by tumor necrosis factor and endotoxins. Presumably, tumor necrosis factor induces tissue factor expression on the surface of activated monocytes and possibly by exposure to subendothelially localized tissue factor in blood. 55 Although the intrinsic system does not induce DIC, it may contribute to hypotension. This triggers the coagulation process (Fig. 46–4), resulting in consumption of factors I, II, V, and VIII and platelets. Supposedly, thrombi and fibrin are deposited in the microcirculation of vital organs, interrupting their blood flow.

FIGURE 46–4 Schematic representation of primary fibrinolysis and fibrinol-ysis secondary to disseminated intravascular coagulation (DIC). Although ?-aminocaproic acid (EACA) inhibits primary fibrinolysis, it also inhibits secondary fibrinolysis, one of the main defenses against DIC. (From Miller52)

In an attempt to counteract the hypercoagulable state, the fibrinolytic system is activated to lyse the excessive fibrin almost simultaneously; this is termed *secondary fibrinolysis.* Primary fibrinolysis is very rare and refers to activation of the fibrinolytic system without concomitant DIC (Fig. 46–4). With secondary fibrinolysis, activation of plasminogen to plasmin (fibrinolysis; see Fig. 46–4) is a protective mechanism that tends to prevent further DIC. With fulminate DIC and subsequent rapid depletion of coagulation factors, plasmin is formed from plasminogen at a rapid rate. The resultant fibrinolysis caused by plasmin creates a paradoxical state. Fibrinolysis does protect against further DIC but may also contribute to the severity of the bleeding diathesis. Plasmin digests fibrinogen, further reducing the fibrinogen level. The digestion of fibrinogen results in the formation of fibrin-split products in the serum; the presence of these products indicates fibrinolysis. While the fibrinolytic system is actively trying to counteract DIC in early stages, plasminogen activator activity and plasmin generation rapidly decline, leaving DIC to progress unopposed. 55 It is at this stage that severe morbidity and eventually mortality are likely to occur.

Disseminated intravascular coagulation should not be considered a distinct disease entity but rather a sign of another disease. Accordingly, DIC has been associated with nearly all life-threatening diseases. Any condition in which tissue damage is sufficient to release tissue products or toxins into the circulation can be associated with DIC. Should enough thromboplastin lodge in the circulating blood, the result is massive focal necrosis or more generalized activation of the coagulation system.

That DIC is a primary cause of organ failure, as suggested earlier, is an attractive hypothesis but has been challenged. Attar et al 56 observed probable DIC in 294 patients with shock but found no fibrin deposits in 52 of them examined at autopsy. Furthermore, survival rates of patients who have DIC associated with hypovolemia or septic shock are not increased by the administration of heparin. 57, 58 Mant and King 59 provided an excellent evaluation of 47 patients with severe acute DIC mostly resulting from shock, infections, trauma, hepatic disease, and malignancy. Routine treatment included aggressive therapy of the underlying diseases and administration of blood products and vitamin K when indicated. Of the 47 patients, 12 were treated with heparin; bleeding worsened in seven (58%) and DIC diminished in five (42%). A total of 35 patients did not receive heparin; the DIC diminished in 13 (37%), but overall, 30 patients (86%) died. The investigators felt death could not have been prevented by heparin therapy. Also, microvascular thrombi were not found in 25 patients examined at autopsy. On the basis of these findings, Mant and King 59 provided the following conclusions, which we feel accurately summarize the current knowledge of DIC:

1.
DIC is a relatively uncommon entity.
2.
Accompanying microvascular thrombosis is uncommon.
3.
DIC rarely causes significant organ damage and infarction.
4.
Accompanying large vessel thrombosis is relatively common but is probably not primarily caused by DIC.
5.
Although bleeding is common, severe bleeding usually originates from sites of local disorder (e.g., lacerated liver).
6.
Heparin is seldom useful and often causes hemorrhage.
7.
DIC is associated with high mortality primarily because of the severity of the patient‘s underlying disorder.
8.
DIC is perhaps best regarded as an incidental preterminal event in most patients.

More recently, Fourrier et al 60 confirmed the aforementioned statements and concluded that DIC is a strong predictor of death. These investigators found that measurements of antithrombin III, protein C, and protein S levels were consistent with sustained DIC and inhibition of fibrinolysis. In fact, they stated that initial antithrombin III levels were the best predictor of death in septic patients.

Hemolytic Transfusion Reaction

The appearance of a hemorrhagic diathesis after blood transfusion should signal the possibility of a hemolytic transfusion; this entity is discussed later in this chapter.

Diagnosis and Treatment of a Hemorrhagic Diathesis After Whole Blood Transfusions

Although treatment is more likely to be successful when the cause of the bleeding problem has been identified, precise diagnosis is often difficult. The more common, readily available laboratory tests seldom yield information precise enough to establish an accurate diagnosis. 52 For example, thrombocytopenia is most likely on a dilutional basis but could be secondary to DIC alone or DIC associated with a hemolytic transfusion reaction. Laboratory tests offering more precise information, such as euglobulin lysis time, often are not readily available or take too long to perform to be practical in an emergency situation.

When the problem of a clinical hemorrhagic diathesis associated with blood transfusions occurs, one approach is to obtain a blood specimen on which the following tests can be performed: platelet count, partial thromboplastin time, plasma fibrinogen level, and observation of a clot for size, stability, and lysis and of the plasma for evidence of hemolysis. For many years, thromboelastography and assessment of the viscoelastic properties of plasma (Sonoclot) 61 have occasionally been recommended for monitoring the influence of blood loss and transfusions on coagulation. However, these techniques have not been widely accepted.

Although many other diagnostic approaches probably are equally valid, the preceding approach works well for me. Provided that the partial thromboplastin time is 1.5 times normal or more increased and other tests are normal, the bleeding is probably a result of very low levels of factors V and VIII. This can be treated with FFP, which contains all the coagulation factors except platelets. Although the preceding situation is a nice textbook description, I have never observed clinical situation involving blood transfusions in which the partial thromboplastin time was increased without the presence of thrombocytopenia.

As indicated, dilutional thrombocytopenia in association with DIC is the most likely cause of bleeding from blood transfusion. 49, 52 When the platelet count is less than 100,000/mm3, a bleeding problem is likely to develop (see Table 46–4); therefore, platelets are ordered. Unfortunately, the common delay between ordering and receiving the platelets dictates that they be ordered before the appearance of a hemorrhagic diathesis. Our rule of thumb is based on the fact that a bleeding diathesis probably will develop after infusion of 20 units of stored blood in healthy patients and after lesser amounts in debilitated or small patients (Fig. 46–5). Therefore, platelets should be ordered after infusion of 9 or 10 units of blood when several more will probably be required. Ideally, the platelets are available when 20 to 25 units of blood has been administered. The timing of ordering platelets in relation to when they will actually be required depends on the capabilities and the limitations of the local blood bank, which differ widely throughout the United States. Thus, the anesthesiologist and the surgeon must consult the blood bank before the need for platelets or any other blood component emerges.

TABLE 46–4. Properties of Whole Blood and Packed Red Cell Concentrates Stored in CPDA-1
FIGURE 46–5 Correlation between units of blood administered and percent of patients who had a hemorrhagic diathesis. The numbers in parentheses represent the number of patients at each data point. (From Miller180)

Whether platelets are administered in the form of fresh blood, platelet-rich plasma, or platelet concentrates depends on volume replacement requirements, personal preference, and availability of laboratory personnel. Fresh blood (<6 hours old) supplies the greatest number of platelets per donation. More than 80 percent of the platelets can be given by platelet-rich plasma, which has half the volume of a unit of blood. However, because most blood banks advocate giving patients only those components that are necessary, platelet concentrates are frequently recommended. The remainder of the unit of blood, such as RBCs, plasma, and albumin, can be saved for other patients. Platelet concentrates are contained in a 50-mL unit and provide about 70 percent of the platelets in a unit of blood. In a 70-kg person, about 10 units of platelet concentrates is required to increase the platelet count by 100,000/mm3 Although platelet concentrates are usually recommended, when a hypovolemic patient also needs replacement of RBCs, albumin, and other plasma coagulation factors, the infusion of fresh whole blood, if available, may be more practical than trying to infuse each of the components individually.

Although logistically difficult to obtain, fresh blood has been found to be extremely effective in treating transfusion-induced coagulopathies. My personal and subjective observations in Vietnam indicated that fresh blood (i.e., 6 hours or less and unrefrigerated blood) had a dramatic effect in patients with extensive hemorrhage. 49 About 20 years later, Lavee et al 62 found that 1 unit of fresh whole blood was as effective as, if not superior to, 8 to 10 platelet units. In 1996, Erber et al, 63 used fresh unrefrigerated whole blood in surgical patients with ongoing extensive bleeding despite adequate component replacement therapy and adequate surgical hemostasis. An accompanying editorial expressed caution and described the unfortunate problems with conducting a larger trial with fresh blood. 64 I believe that fresh blood also contains unidentified factors that make it far more effective than blood components.

Determining the plasma fibrinogen level is useful because this coagulation factor does not decrease in bank blood. Therefore, if the *in vivo* plasma fibrinogen level is low (<150 mg/100 mL), this is not a result of a dilutional coagulopathy and strongly suggests DIC. DIC is likely with thrombocytopenia, hypofibrinogenemia, and lysis of a clot within 2 hours. 52 Unfortunately, fibrinogen levels in packed RBCs decrease with increasing storage time. As a result, hypofibrinogenemia occurs on a dilutional basis when multiple units of packed RBCs are given. 65 Thus, the separation of thrombocytopenia on a dilutional basis versus DIC cannot be accomplished by the use of fibrinogen level when packed RBCs have been given. Perhaps more specific readily available tests will be available in the future, 60 which will be especially important with potential therapies that are currently unavailable (e.g., monoclonal antibodies, anti–tumor necrosis factor antibodies, recombinant interleukin/receptor antagonists). 55 As indicated previously, the most effective treatment of DIC is removal or treatment of the basic disease process causing the DIC; these diseases usually cause DIC by release of damaged tissue products into the circulation. For example, the DIC associated with abruptio placentae usually ceases after emptying of the uterus and restoration of blood volume.

?-Aminocaproic acid (EACA) inhibits the formation of plasmin and attenuates fibrinolysis (see Fig. 46–4). Obviously, EACA should not be used in the treatment of DIC. Blocking the fibrinolytic system and having the coagulation system activated have resulted in disseminated thrombosis. Because primary fibrinolysis is extremely rare other than in prostatectomy and liver transplantation 66 (Ch. 55), EACA probably should not be given unless the preceding diagnosis is clearly established after expert consultation. As indicated, administration of EACA (for what was thought to be primary fibrinolysis but was really fibrinolysis secondary to DIC) can result in severe thrombotic episodes. Because the tests to distinguish primary from secondary fibrinolysis are not usually available, the risks of thrombotic episodes from EACA can be minimized by concomitant administration of heparin. Obviously, this becomes a complicated coagulation problem that exceeds the expertise of most surgeons and anesthesiologists.

Drugs Used to Improve Hemostasis

In addition to EACA, three other drugs have been recommended for perioperative coagulation problems. Two of those drugs have received special attention. The first is desmopressin (DDAVP), which is a synthetic analogue of the antidiuretic hormone vasopressin. It increases factor VIII and von Willebrand factor. It is, therefore, well established therapy for hemophilia and von Willebrand disease. It has also been shown to reduce blood loss and transfusion requirement in patients with normal preoperative coagulation status who are undergoing spinal or cardiac surgery. However, the ultimate role of DDAVP remains to be determined. 66, 67, 68 DDAVP can cause hypotension, hyponatremia, and increased platelet adhesion.

Another drug is aprotinin, a serine protease inhibitor that inhibits fibrinolysis and improves platelet function. 69 It has been used to decrease blood loss in multiple surgical procedures, including cardiopulmonary bypass. However, its ultimate place in the treatment of coagulopathies has not been established.

The third drug is tranexamic acid, which is also an antifibrinolytic drug. Two studies found a decreased blood loss from total knee arthroplasty. 70, 71 Presumably, release of the pneumatic tourniquet releases fibrinolytic material, which is inhibited by tranexamic acid.

A large meta-analysis using perioperative blood transfusion as the outcome in cardiac surgery concluded that aprotinin and tranexamic acid, but not DDAVP, decreased the exposure of patients to allogeneic blood transfusion perioperatively. 72

Clearly, the ultimate use of these drugs is evolving.

Diagnosis and Treatment of Hemorrhagic Diathesis After Packed RBC Transfusions

Most studies have examined the influence of massive transfusion of whole blood on coagulation because many trauma centers use whole blood. However, packed RBCs (see Packed Red Blood Cells) are often given because whole blood may not be available. With much less plasma, dilution of certain coagulation values may be more profound with the use of packed RBCs rather than whole blood.

Murray et al 65 specifically examined the question of using packed RBCs for major blood loss. In general, the direction of coagulation changes was similar to that seen with whole blood, with one major exception. With use of packed RBCs, fibrinogen levels decreased significantly in contrast to use of whole blood, in which fibrinogen levels remained unchanged unless DIC was present (Fig. 46–6). Although all the coagulation factors decreased, the decrease was less than expected from dilution. The researchers felt that factors such as VIII are probably stored in endothelial cells and released from the endothelium during surgical stress. When packed RBCs are used to replace major blood loss, the cli-nician may be tempted to give FFP prophylactically. However, Murray et al 65 specifically recommended not following the policy; they stated that FFP was needed only when prothrombin time and partial thromboplastin time were at least 1.5 times normal and fibrinogen levels were less than 75 mg/dL. These recommendations are similar to those stated in the section Fresh Frozen Plasma. More recently, Leslie and Toy 73 provided more specific guidelines when packed red cells are used for massive transfusions. They believed that when 12 or more units of packed red cells or cell-saver blood had been given, coagulation factors (i.e., FFP) were necessary. Those patients who received 20 or more units often required platelet therapy, a finding identical to that of patients given whole blood.
FIGURE 46–6 Decreases in fibrinogen level as blood volume is replaced with Adsol-packed red blood cells and crystalloid solutions. Each patient is represented by a solid line. (From Murray et al65)

An algorithm for the evaluation and initial therapy of a patient with a suspected coagulopathy is given in Figure 46–7.
FIGURE 46–7 Algorithm of the evaluation and initial therapy of the patient with suspected perioperative coagulopathy. Evaluation is based on the clinical scenario and is readily affected by type and location of injury, the amount of fluid administered, and the age and body temperature of the patient. DDAVP, trademark for preparation of desmopressin acetate; PT, prothrombin time; PTT, partial thromboplastin time. (From Habibi et al20)

Citrate Intoxication and Hyperkalemia

Citrate intoxication is not caused by the citrate ion per se, but because citrate binds calcium. Thus, the signs of citrate intoxication are those of hypocalcemia, that is, hypotension, narrow pulse pressure, and elevated intraventricular enddiastolic pressure and central venous pressure. However, if circulatory volume is reasonably well maintained, these cardiovascular changes do not occur unless ACD blood is given at a rate greater than 150 mL/70 kg/min, or about 1 unit of blood per 5 minutes in an average-sized adult. With newer preservatives with less citrate, intoxication is even less likely.

Decreased levels of serum ionized calcium do occur in low flow states, especially in out-of-hospital cardiac arrests. 74 These decreases have no predictable relationship to total plasma concentration. A possible conclusion is that if blood is given to such a critically ill patient, the serum ionized calcium levels may decrease even more. However, Drop and Laver 75 found that these abnormally low concentrations of ionized calcium were not readily corrected by intravenous administration of calcium salts in doses generally recommended (i.e., 1.0 g of calcium chloride). However, ionized calcium levels returned toward normal when hemodynamic status was improved by increasing the isoproterenol infusion rate. The beneficial effect of isoproterenol probably indicates that mobilization ionized calcium from body stores may be inadequate because of abnormal distribution of blood flow. Thus, improvement of a patient‘s circulatory status (blood transfusion) may ultimately increase ionized calcium levels without calcium administration. If calcium is given to patients with low-output states, calcium chloride may have to be administered at rates as high as 1.5 mg/kg/min. Drop and Laver 75 recommended that this amount of calcium chloride not be given without close monitoring of serum ionized calcium levels, because a constant relationship with total serum calcium level is not established. With the absence of ionized calcium electrodes, the well-known inotropic stimulation

may lead the clinician to administer calcium any time evidence of inadequate cardiac output is present, especially when multiple blood transfusions have been given.

Thus, even in patients with low-output states, I believe that emphasis should be placed on correcting the underlying disorder (i.e., hypovolemia) and that calcium administration is rarely necessary. 76 The reason that serum ionized calcium levels rapidly return to normal immediately after cessation of the blood transfusion (Fig. 46–8) probably is rapid citrate metabolism by the liver and rapid calcium mobilization from available endogenous stores. Hypothermia, liver disease, liver transplantation, and hyperventilation increase the possibility of citrate intoxication. In fact, the appearance of severe hypocalcemia during liver transplantation is well documented (Ch. 55). Obviously, the combination of infusion of large amounts of citrate (i.e., via blood transfusions) and of reduced metabolism from absent or reduced liver blood flow (i.e., in the anhepatic phases of liver transplantation) leads to citrate intoxication. As a result, calcium infusions are common during liver transplantation (Kelley S, personal communication, 1999). The rate of citrate metabolism is decreased by 50 percent when body temperature is decreased from 37° to 31°C. Excluding these conditions, infusion of more than 1 unit of blood every 10 minutes is necessary for ionized calcium levels to begin to decrease. Even at these rates of infusion, ionized calcium levels do not decrease enough to cause bleeding. As indicated previously, if a hemorrhagic diathesis starts after administration of blood, low calcium levels are not part of the differential diagnosis.
FIGURE 46–8 Correlation between the time during and after citrated whole blood infusion and serum-ionized calcium (mM/L.). (From Denlinger et al181)

As evidenced from the preceding discussion, citrate intoxication is obviously rare. Serum potassium levels may be as high as 19 to 30 mEq/L in blood stored for 21 days. Although hyperkalemia is occasionally reported, 77 large amounts of blood must be given. For significant hyperkalemia to occur clinically, bank blood must be given at a rate of 120 mL/min or more. The fact that such rapid infusion rates of blood are required for the production of hyperkalemia suggests that the potassium ion must leave the intravascular spaces by diffusion into extravascular spaces, by reuptake into red cells, or via the kidneys. As with citrate intoxication, hyperkalemia is rare, and this again rules against the routine administration of calcium. In fact, calcium may cause cardiac arrhythmias, particularly in patients anesthetized with halothane. Calcium administration should be based on diagnostic signs of hyperkalemia (peak T wave).

Even though it is reported to be irritating to veins, 10 percent calcium chloride provides three times more calcium than an equal volume of 10 percent calcium gluconate because chloride has a molecular weight of 147 and gluconate a molecular weight of 448.

Temperature

Administration of unwarmed blood that has been stored at 4°C can decrease the recipient's temperature. If the temperature decreases to less than 30°C, ventricular irritability and even cardiac arrest may occur. This can be prevented by warming the blood to body temperature before transfusion. I believe that there are more subtle reasons for warming all blood, even in patients receiving only 1 to 2 units intraoperatively. Because of the cool temperature of the operating room, body temperature often decreases, particularly in patients undergoing extensive abdominal surgery 78 (Ch. 37); administration of cold blood further decreases temperature. A decrease in body temperature as small as 0.5 to 1.0°C may induce shivering postoperatively; this in turn may increase oxygen consumption by as much as 400 percent. To meet the demands of elevated oxygen consumption, cardiac output must be increased. Is this too much stress for the patient with marginal cardiac reserve? More studies are required to confirm this fear.

Perhaps the safest and most common method of warming blood is to pass it through plastic coils immersed in warm water (37° to 38°C) bath. With increased use of packed RBCs (e.g., in contrast to whole blood), other methods of warming blood have been suggested. For example, Zorko and Polsky 79 added normal saline warmed to 45°C to packed RBCs. Clearly, maximal flow rates are achieved with diluted cells not passed through a warmer, but delivery temperature is higher when passed through a warmer (Table 46–6). Despite the aforementioned well-documented information, five cases of overheated hemolyzed blood have been reported to the FDA during the past 10 years. 80 A variety of warming techniques have been reviewed by Iserson and Heustis. 81

TABLE 46–6. Four Methods of Warming Packed Red Blood Cells

Acid-Base Abnormalities

The pH of most storage media is very acidotic (CPD, 5.5). When this solution is added to a unit of freshly drawn blood, the pH of the blood immediately decreases to approximately 7.0 to 7.1. As a result of accumulation of lactic and pyruvic acids by RBC metabolism and glycolysis, the pH of bank blood continues to decrease to about 6.9 after 21 days of storage. A large portion of the acidosis can be accounted for by the PCO2 of 150 to 220 mm Hg. The PCO2 is high mainly because the plastic container of blood does not provide an escape mechanism for carbon dioxide. With adequate ventilation in the recipient, the high PCO2 should be of little consequence. Even when the PCO2 is returned to 40 mm Hg, metabolic acidosis is still present in blood (see Table 46–4), and some clinicians empirically recommend giving alkalizing agents. Also, other reasonably well-controlled clinical studies have indicated that not only is empirical administration of sodium bicarbonate not indicated but it may also actually be unwise without concomitant analysis of arterial blood for PCO2 and pH. 82 Miller et al 83 found that the metabolic acid-base response to blood transfusion was variable (Fig. 46–9). Actually, blood transfusions provide a substrate, namely citrate, in large quantities for the endogenous generation of bicarbonate, and this accounts for the significant incidence of metabolic alkalosis after blood transfusions. 82 Therefore, there is little logic in the empirical administration of bicarbonate for prophylactic treatment of an unpredictable acid-base abnormality. Bicarbonate therapy should be initiated when metabolic acidosis is diagnosed. This can be accomplished by analysis of arterial blood for PCO2 and pH. When a suitable artery cannot be palpated because an extremity is inaccessible during a particular operative procedure, peripheral venous blood can be used for PCO2 and pH determinations. During anesthesia, peripheral venous blood usually has a PO2 of more than 60 mm Hg. Therefore, because this blood is arterialized, PCO2 and pH can be determined, and the amount of bicarbonate required can be calculated. 84
FIGURE 46–9 Correlation between the amount of blood administered (mL) and corrected base excess intraoperatively. (From Miller et al83)

Although treatment of metabolic acidosis with bicarbonate has been viewed as being important, can any harm result from excessive bicarbonate administration or from metabolic alkalosis (Chs. 38 and 75)? Actually, large doses of bicarbo-nate (e.g., 1–10 mEq/kg) can interfere with coagulation, as evidenced by prolonged prothrombin and thrombin clotting times. 85 Also, alkalosis augments a left shift of the oxygen dissociation curve. Because of citrate metabolism, exogenous bicarbonate, and administration of lactated Ringer solution, metabolic alkalosis commonly occurs after infusion of several units of blood. Thus, bicarbonate administration should be reserved for patients in whom severe metabolic acidosis (base excess >7 mEq/L) has been diagnosed.

Infusion of Microaggregates

In 1970, Moseley and Doty 86 demonstrated that amounts of clot and debris in bank blood increased with duration of storage. Some of this particulate matter is not filtered by the standard 170-m filter during routine transfusion and enters the recipient‘s blood stream. 86 These authors suggest, therefore, that respiratory insufficiency in patients with severe trauma and hemorrhage (so-called shock lung) or adult respiratory distress syndrome may be a result of the accumulation of this particulate material in the lungs, resulting in vascular obstruction. Several filters with pore sizes less than 40 m (micropore filters) are now available to remove microaggregates from bank blood. When massive transfusions of stored blood are involved, the use of micropore filters, in theory, should eliminate this important contributor to the development of adult respiratory distress syndrome. However, the evidence supporting the preceding concept and the need for micropore filters during massive transfusions of stored blood is unproved.

More recent information suggests that the thrombocytopenia associated with transfusions can be attenuated by the use of micropore filters. 87, 88 Also, the removal of white blood cells may reduce the infectivity of blood. 89 In fact, it is likely that prefiltered blood designed to remove most of the white blood cells will be routinely provided by blood banks in the future. Lastly, newer preservative solutions will probably eliminate microaggregates. Clearly, the use of micropore filters is evolving and is not resolved. 90

Transfusion Reactions

Hemolytic Transfusion Reaction

Since 1975, the FDA has required that all fatal reactions occurring in blood recipients or donors be reported within 24 hours by telephone, or within 7 days in writing, by all FDA-registered transfusion services. In the 10-year period from 1976 to 1985, 328 deaths have been reported and analyzed. 91 Of these deaths, 159 were acute from hemolytic reactions and 23 from delayed reactions. Of the 159 deaths due to acute hemolytic reaction, 137 were caused by errors involving ABO incompatibility. More than half of these mistakes occurred after the blood had been issued by the blood bank and were committed by nurses and physicians in the operating room, emergency room, or ward. The incidence of hemolytic transfusion reaction is in the range of 1/300,000 to 1/700,000 RBC transfusions. 92, 92 However, when delayed hemolytic reactions (discussed in a later section) are included, the incidence of ABO-incompatible RBC transfusion is much more frequent. 94 Even though the incidence is low, the anesthesiologist must know the principles of recognizing and treating hemolytic transfusion reactions because of the high morbidity and mortality rate. One of the most catastrophic transfusion reactions is that arising from intravascular hemolysis. Intravascular hemolysis occurs when there is a direct attack on transfused donor cells by recipient antibody and complement. Such a reaction can occur from infusion of as little as 10 mL of blood. 95 Mortality may occur in 20 to 60 percent of those patients with severe symptomatic hemolytic reactions, and these deaths usually result from ABO blood group incompatibility between the donor and the patient. Hemolytic transfusion reactions involving extravascular RBC destruction are generally less serious than those of the intravascular variety. In these cases, recipient antibody coats but does not immediately hemolyze the transfused RBCs. Destruction occurs primarily in the reticuloendothelial system.

Signs and Symptoms

The clinical consequences of incompatible blood transfusions are very serious and yet quite variable. Factors include volume of transfused blood, number of antigenic sites on the red cell membrane, and activity of the reticuloendothelial system. The properties of the antibody, including concentration and ability to activate complement, are also important.

The classic signs and symptoms (Table 46–7) of a hemolytic transfusion reaction—chills, fever, chest and flank pain, and nausea—are masked by anesthesia. Under general anesthesia, the only signs may be hemoglobinuria, bleeding diathesis, or hypotension. In my and Huh and Lichtiger's experience 96 with six and four hemolytic transfusion reactions, respectively, the presenting sign was hemoglobinuria in nine of the ten cases. As little as 50 mL of incompatible blood may exceed the binding capacity of haptoglobin, which is a protein that can bind about 100 mg of hemoglobin per 100 mL of plasma. When hemoglobin not exceeding this amount is injected or liberated into the blood stream, the hemoglobin circulates as a complex with haptoglobin, which is cleared by the reticuloendothelial system (Fig. 46–10). A sample of plasma that contains 2 mg/dL of hemoglobin is faintly pink or light brown. When the level of hemoglobin reaches 100 mg/dL, then the plasma is red. When the level of plasma hemoglobin reaches 150 mg/dL, hemoglobinuria occurs. In general, the quantity of the free hemoglobin in the plasma is correlated with the volume of incompatible blood transfused. Thus, the symptomatology can be so alarming that cessation of blood is indicated, even if hemoglobin is not seen in plasma. Laboratory tests that should be performed if hemolytic transfusion reaction is suspected include serum haptoglobin, plasma and urine hemoglobin, bilirubin, and direct antiglobulin determinations. The direct antiglobulin test can confirm the presence of hemolytic transfusion reaction because it shows that there is antibody attached to transfused donor red blood cells. 97

TABLE 46–7. Frequency and Signs and Symptoms From Hemolytic Transfusion Reactions in 40 Patients
FIGURE 46–10 Schematic representation of what happens to hemolyzed erythrocytes as a result of the administration of incompatible blood.

Treatment

If a hemolytic reaction is suspected, blood and urine samples should be sent to the laboratory for examination. The blood bank should check all paperwork to ensure that the correct blood component was transfused to the patient. Laboratory tests should be performed to determine the presence of hemoglobinemia: a direct antiglobulin test, repeat compatibility testing, repeat other serologic tests (i.e., ABO and Rh) and analysis of urine for hemoglobinuria.

Although there are several consequences of intravascular hemolysis, mainly the renal and coagulation systems are affected. The exact cause of acute renal failure from intravascular hemolysis is controversial, but the most common hypothesis is that hemoglobin in the form of acid hematin precipitates in the distal

tubule and causes mechanical tubular blockage. The magnitude of the precipitation probably is inversely related to the volume of urine flow and its pH. The primary emphasis of therapy should be directed toward maintaining urinary output in excess of 75 mL/h by generous administration of intravenous fluids and diuretics. My approach is summarized in Table 46–8 and includes the administration of lactated Ringer solution to maintain the central venous pressure between 10 and 15 cm H2 O while initially administering 12.5 to 50 g of mannitol. If ineffective, then the dose of mannitol may be increased and/or the use of more potent diuretics, such as furosemide, which increases blood flow to the renal cortex, may be required to maintain adequate urinary output. Alkalinization of the urine to prevent precipitation of acid hematin in the distal tubules is of questionable value but is easy and therefore recommended. DIC commonly occurs with hemolytic transfusion reactions, probably because RBC stroma is severed, releasing erythrocytin, which activates the intrinsic system of coagulation. This activated coagulation leads to fibrin formation. Subsequently, platelets and factors I, II, V, and VII are consumed. As soon as a hemolytic transfusion reaction is recognized, platelet count, prothrombin time, and partial thromboplastin time should be determined to provide baseline values with which subsequent laboratory values can be compared. Hypotension during a hemolytic transfusion reaction may be due to activation of the kallikrein system. 98 After a series of reactions, plasma kininogen is converted to bradykinin, a potent vasodilator that can cause hypotension.

TABLE 46–8. Steps for the Treatment of a Hemolytic Transfusion Reaction

Another approach to treatment of a severe hemolytic transfusion reaction has been proposed by Seager et al, 99 who postulated that the kidneys might be spared from exposure to massive amounts of hemolyzed red cells by removing all blood from a patient and replacing it with compatible blood. This was accomplished in a patient who had received 3,000 mL of incompatible blood by hemodilution by use of an extracorporeal circuit. Because the patient had rapid recovery of urinary function, this method shows much promise.

In summary, hemoglobinuria or hemolysis should be assumed to be a hemolytic transfusion reaction until proved otherwise. The steps outlined in Table 46–8 should be taken when the diagnosis is suspected or confirmed.

Delayed Hemolytic Transfusion Reaction (Immune Extravascular Reaction)

As described earlier, an immediate hemolytic transfusion reaction often is a dramatic event because the concentration of the antibody is high enough to cause immediate and appreciable RBC destruction. However, in many cases of hemolytic transfusion reaction, the transfused donor cells may survive well initially but after a variable delay (2–21 days) is hemolyzed. 100, 101 This type of reaction occurs mainly in recipients sensitized to RBC antigens by previous blood transfusions or pregnancy. As a result, this type of delayed reaction is more common in females who have a known disposition of alloimmunization. These reactions are delayed hemolytic transfusion reactions and are those in which the level of antibody at the time of transfusion is too low to be detected or too low to cause RBC destruction. RBC destruction occurs only when the level of antibody is increased after a secondary stimulus (anamnestic response). These delayed reactions are often manifested only by a decrease in the posttransfusion hematocrit value. However, jaundice and/or hemoglobinuria can occur in these patients and can also cause some impairment in renal function, but only rarely do they lead to death. Unlike immediate reactions, antibodies most commonly involved in delayed hemolytic reactions are those in the Rh and Kidd systems rather than the ABO system. Although improved blood banking procedures have decreased the incidence of immediate hemolytic transfusion reactions, the delayed hemolytic reaction may not be preventable, because pretransfusion testing is unable to detect very low levels of antibody present in potential blood recipients.

Although impairment of renal function is uncommon, the surgical team should include in their differential diagnosis a delayed hemolytic transfusion reaction in any patient who has an unexplained decrease in hematocrit 2 to 21 days after a transfusion, even without obvious manifestation of hemolysis. This is especially important in a postoperative patient when the decrease in hematocrit value is thought to be from blood loss and may be an important criterion as to whether additional surgery is necessary.

Nonhemolytic Transfusion Reactions

These reactions to blood transfusions usually are not serious and are either febrile or allergic in nature. On occasion, fever could be the first sign of a hemolytic reaction or of bac-terial contamination. If the

temperature increase is more than 1°C, a hemolytic reaction should be considered. 93 Bacterial contamination usually occurs with transfusion of platelets.

For less serious febrile reactions, the most common adverse reactions to blood transfusions are the febrile reactions. The symptoms consist of chills, fever, headache, myalgia, nausea, and nonproductive cough occurring shortly after blood transfusion. Less frequently, the patient may have hypotension, chest pain, vomiting, and dyspnea. Even pulmonary infiltrations with x-ray evidence of prehilar nodule formation and lower lung infiltrates along with overt pulmonary edema have been reported. 102 Because febrile reactions obviously involve fever, they can be easily confused with a hemolytic transfusion reaction. A direct antiglobulin test readily differentiates a hemolytic reaction from a febrile reaction because this test rules out the attachment of an RBC antibody to transfused donor RBCs.

There is no clear consensus on whether the transfusion should be terminated when a febrile reaction occurs. 93, 103, 104

Most allergic transfusion reactions are mild and are considered to be caused by the presence of foreign protein in the transfused blood. The most common symptom is urticaria associated with itching. Occasionally, the patient has facial swelling. Allergic reactions occur in about 3 percent of all transfusions. When these reactions are accompanied by fever or any other symptoms suggestive of a serious hemolytic reaction, it is not necessary to discontinue the transfusion. Antihistamines are used to relieve the symptoms of the allergic reaction. Infrequently, a more severe form of allergic reaction involving anaphylaxis occurs in which the patient has dyspnea, hypotension, laryngeal edema, chest pain, and shock. These are anaphylactic reactions caused by the transfusion of IgA to patients who are IgA deficient and have formed anti-IgA. This type of reaction does not involve red cell destruction and occurs very rapidly, usually after the transfusion of only a few milliliters of blood or plasma. The patients who experience these anaphylactic reactions must be given transfusions with washed red blood cells from which all traces of donor IgA have been removed, or with blood lacking the IgA protein. 105

There are many other rare transfusions reactions, which have been reviewed by several authors.

Infectivity of Blood

With the introduction of transfusion-induced AIDS, the infectivity by homologous blood transfusion has received renewed attention. In fact, for many years, blood banks use one or two tests (i.e., syphilis and hepatitis B surface antigen) to screen blood. In recent years, many more tests have been added (Table 46–9). Overall, blood is probably safer than it has been for years.

TABLE 46–9. Infectious Disease Testing for Blood Transfusions

Hepatitis

When blood transfusions became a reality in the 1940s, viral hepatitis was recognized as a major complication. Now, in the past 10 years, the incidence of viral hepatitis has dramatically decreased. Nevertheless, when it occurs, it is very serious. Classically, icteric hepatitis develops 50 to 180 days after a blood transfusion and has a variable clinical course, ranging from asymptomatic to fatal. However, two to five anicteric cases occur for every case of overt icteric hep-atitis. Generally, the diagnosis of acute anicteric posttransfusion hepatitis is made with the observation, between 14 and 180 days after transfusion, of two consecutive elevations (at least 14 days apart) of the recipient‘s alanine aminotransferase level. Other possible causative factors, such as congestive heart failure, alcohol, and certain drugs that can mimic or simulate viral hepatitis, obviously must be considered. Both transaminase elevations must be at least 2 standard deviations above the geometric mean value for healthy persons.

Serologic requirements for the diagnosis of hepatitis B include the *de novo* appearance of hepatitis B surface antigen or hepatitis B surface or core antibody. Hepatitis A antibody seroconversion is considered evidence for hepatitis A infection. However, 90 percent of posttransfusion hepatitis is caused by the hepatitis C virus. Less than one-third of these patients develop jaundice. 106 To determine their ultimate fate, Tong et al 106 monitored 131 patients with chronic posttransfusion hepatitis C for several years and found the following incidence of signs, symptoms, and conditions:

1.
Fatigue (67%)
2.
Hepatomegaly (67%)
3.
Chronic hepatitis (23%)
4.
Chronic active hepatitis (51%)
5.
Hepatocellular carcinoma (11%)

On follow-up, it was found that 20 patients had died, from

1.
Complications of cirrhosis (eight patients)
2.
Hepatocellular carcinoma (11 patients)
3.
Chronic active hepatitis-pneumonia (one patient)

Before 1983 to 1985, the overall incidence of posttransfusion hepatitis ranged from a low of 3 percent to a high of 19 percent, depending on the institution and the location (e.g., donors from large cities have a higher incidence of the hepatitis virus). In most areas, the incidence of hepatitis has ranged from 3 to 10 percent. Since 1985, the incidence of posttransfusion hepatitis has decreased, probably for three reasons. First is improved donor screening. In 1984, donors who were in a high-risk category for AIDS were requested not to donate blood on a volunteer basis. Second, in 1985 all donor blood was tested for antibodies to the AIDS virus (see Acquired Immunodeficiency Syndrome). Third, a specific test for hepatitis C was developed. Specifically, molecular techniques were used to derive clones from the genome of hepatitis C. The derived proteins from these clones were used to develop an enzyme-linked immunosorbent assay to detect antibodies to hepatitis C. As a result, the incidence of posttransfusion hepatitis is lower by far than it has been for more than 20 years (Table 46–10). 107 Despite the effectiveness of this test, donor infectivity is important as a screening device. Demographics of infectivity among donors is variable and is especially frequent in intravenous drug users. 108 Finally, it should be remembered that many blood components, such as packed red cells, FFP, and platelet concentrates, also transmit hepatitis at an incidence equal to that of whole blood.

TABLE 46–10. Percentage Risk of Transfusion-Transmitted Infection With a Unit of Screened Blood in the United States

There has been a concern about the relationship between transfusions and hepatitis delta virus. This virus is a defective RNA virus that cannot survive on its own and requires the helper function of a DNA virus, hepatitis B, to support its replication and expression. Therefore, the hepatitis delta virus can infect only persons with hepatitis B, either one in whom infections occur simultaneously or one who is a hepatitis B carrier. 109 This is a very virulent form of hepatitis, which can transform a mild chronic hepatitis B infection to severe progressive chronic active hepatitis and cirrhosis. Delta hepatitis can be prevented by vaccinating susceptible or high-risk individuals, such as anesthesiologists (Ch. 84), with hepatitis B vaccine. However, the delta virus can be transmitted by blood transfusions. Rosina et al 110 concluded that screening donors for hepatitis B provides a high degree of safety in preventing infection with hepatitis delta virus but that the risk is greater in patients who are already carriers of hepatitis B. They concluded that hepatitis B carriers should be given only blood derivatives from a single donor or minipool donors.

Acquired Immunodeficiency Syndrome

Acquired immunodeficiency syndrome is characterized by severe depression of cellular immunity. Clinically, opportunistic infections and/or Kaposi sarcoma appears, progressing to debility and death. Pattern of transmission is similar to that of hepatitis B. Although AIDS is most frequently transmitted by intimate homosexual contact and intravenous drug abuse, nevertheless, whole blood, plasma, blood cellular

products, or clotting factors can transmit AIDS. 111 Several measures have been recommended to decrease the chances that donor blood will be infected with AIDS. Blood banks have instituted procedures to discourage members of high-risk groups from donating blood. Designated donors and surrogate testing have been recommended. 112, 113 Despite these measures, there were hundreds of cases of transfusion-transmitted AIDS. In March 1985, all donor blood was tested for the presence of antibodies to the AIDS virus (human immunodeficiency virus type 1 [HIV-1]). This testing has dramatically reduced the incidence of transfusion-transmitted AIDS (Table 46–10). 107

Human T-Cell Lymphotropic Virus Type I

Human T-cell lymphotropic virus type I (HTLV-I) can be transmitted by blood transfusions and has been causally associated with adult T-cell leukemia and progressive myelopathy. Cohen et al 114 found that there is a very small risk of HTLV-I infection from transfused blood and blood products that have been screened for antibodies to HIV, but that risk is nearly 10-fold higher than risk of HIV infections. Specifically, they found the risk to be 0.003 percent/U for HIV infection and 0.024 percent/U for HTLV-I infection. Even though there is no firm association between transfusion and leukemia or myelopathy, the decision was made to test all donor blood for antibodies to the HTLV-I virus.

Cytomegalovirus

Asymptomatic chronic infection with cytomegalovirus (CMV) is so common in healthy adults that this agent can almost be viewed as normal flora. CMV survives best within cells and is thought to exist in latent form in the leukocytes of many people with antibodies indicative of earlier infection. CMV causes a heterophil antibody-negative response that closely resembles infectious mononucleosis in many respects. An infectious mononucleosis-like syndrome that can occur 1 to 2 months after open heart surgery is known as the postperfusion syndrome or posttransfusion mononucleosis. The evidence for transmission of CMV is most convincing when the recipient changes from a seronegative state before transfusion to a seropositive state accompanied by the mononucleosis-like illness several weeks after transfusion.

Transfusion-transmitted CMV can cause significant clinical problems in certain patient populations, such as premature neonates, allograph recipients, and patients who have had their spleens removed. 115 To prevent infection in high-risk populations, use of leukocyte-depleted blood, use of frozen deglycerolized RBCs, and screening of donors for the absence of antibody to CMV have been sometimes recommended. The risk of seroconversion is about 0.14 percent overall or 0.38 percent per unit of seropositive donor blood. 116 Wilhelm et al 117 concluded that it is not necessary to provide blood products from CMV-seronegative donors for most patients who receive blood transfusions. They con-tinue to use CMV-seronegative blood to prevent CMV infection in preterm and newborn babies. Whether CMV-negative blood should be used for other immunocompromised patients and pregnant women has not yet been resolved.

Other Transfusion-Associated Infectious Diseases

Although many other infectious diseases can theoretically be transmitted by blood transfusion, only a few are of real concern. They include *Y. enterocolitica* infection, syphilis, and malaria.

During the late 1980s, Tripple et al 118 described seven cases of fatal transfusion-associated *Yersinia enterocolitica* sepsis. These investigators also reviewed the literature and found 26 cases of gram-negative bacterial sepsis with whole blood or packed RBCs. *Y. enterocolitica* is a bacterium that can cause mostly mild gastrointestinal problems. However, in severe cases, sepsis and death can occur. Unfortunately, storage of blood at 4°C in phosphate buffer enhances its growth. Aber 119 suggested that the donor screening process include assessment as to whether gastrointestinal problems occurred within 4 weeks of donation and that the storage time be minimized. More specific recommendations were not provided, although some were suggested by Grossman et al. 120

Posttransfusion syphilis is unlikely because the infective agent cannot survive during storage at 1° to 6°C. The only blood products that have the potential to transmit syphilis are those stored at room temperature. Platelet concentrates are the blood component most likely to be implicated because they commonly are stored at room temperature.

Posttransfusion malaria has never been a significant cause of blood recipient morbidity. Nevertheless, malaria can occur, especially if blood donors at risk of harboring parasites are not excluded. Consequently, blood banks thoroughly question donors for history of travel or migration from areas where malaria is endemic.

Several other diseases have also been reported to be transmitted by blood transfusion, including herpes virus infections, infectious mononucleosis (Epstein-Barr virus), toxoplasmosis, trypanosomiasis, leishmaniasis, brucellosis, typhus, filariasis, measles, salmonellosis, and Colorado tick fever.

The Future of the Infectivity and Testing of Blood

Although the data in Table 46–10 are correct as of 1999, they will change fairly soon. With new tests that identify the nucleic acid of the virus, the "window period" will be reduced to as short as 1 day. This could decrease the incidence of HIV and hepatitis C to 1:1,000,000, making allogeneic blood incredibly safe from an infectivity point of view.

Other Adverse Effects of Blood Transfusion

Transfusion-Associated Graft-Versus-Host Disease

This disease occurs when donor lymphocytes from transfused blood products engraft in the recipient, initiating an immune reaction against host tissue. A generalized rash, leukopenia, and thrombocytopenia occur. Sepsis and death usually result. Irradiation of blood can prevent transfusion-associated graft-versus-host disease from occurring, although there is a report of one case occurring despite leukocyte filtering. 121

Transfusion-Related Acute Lung Injury

This injury manifests as noncardiogenic pulmonary edema resulting from immune reactivity of certain leukocyte antibodies a few hours after transfusion. Specifically, it involves an antigen-antibody mechanism involving human leukocyte antigen and granulocyte antigens. Transfusionrelated acute lung injury is associated with a mortality rate (<10%) much lower than that from the adult respiratory distress syndrome.

Adverse Ocular Reaction

In 1997, 112 cases of bilateral conjunctival erythema were reported to have occurred within 24 hours of transfusion. The Centers for Disease Control and Prevention studied 49 other cases in 1997 and 1998 and concluded that they were toxic reactions to a chemical or material used in the blood collection filtration system, most likely a leukocyte-reducing filter system.

BLOOD COMPONENT THERAPY

Packed Red Blood Cells

In essence, packed RBCs contain the same amount of hemoglobin as whole blood, but much of the plasma has been removed. Thus, the hematocrit value is 40 percent in whole blood and 70 percent in packed erythrocytes (Table 46–13). The position of the American Association of Blood Banks has been that transfusion of whole blood is required primarily for blood loss acute enough to cause hypovolemic shock. More specifically, they state that the primary indication for whole blood is for patients who are actively bleeding and have sustained a loss of greater than 25 percent of their total blood volume. In other words, whole blood provides both oxygen-carrying capacity and blood volume expansion. Less severe degrees of hemorrhage may be effectively treated with packed RBCs, thus retaining the plasma and the components thereof for other patients (see Fig. 46–11). Many blood banks have religiously followed this principle, so that whole blood cannot be obtained in the operating rooms except by special request. In essence, blood bankers are saying that except for a rare situation (i.e., hypovolemic shock), whole blood is not necessary.

TABLE 46–13. Comparison of Whole Blood and Packed Red Blood Cells
FIGURE 46–11 Diagrammatic scheme of separation of whole blood for component therapy.

For the patient who has lost blood and needs both erythrocytes and intravascular volume, what advantage is there in receiving packed erythrocytes instead of whole blood? There are no prospective data that document reduced risk of posttransfusion hepatitis. Furthermore, the incidence of transfusion reactions is not reduced unless “buffy-poor” or previously washed cells are used. It is doubtful whether small plasma and white blood antigenic load are of any benefit. For those patients in whom anaphylactic reactions to IgA develop, the erythrocytes must be completely free of plasma. Finally, the use of packed RBCs does not reduce potassium load unless the erythrocytes are packed immediately before infusion. If the RBCs are packed when the blood is freshly drawn, as is the usual case, the amount of potassium removed is minimal.

Despite all the preceding evidence to the contrary, I believe packed RBCs should still be used instead of whole blood, except in cases of severe hemorrhage. My rule is to use packed RBCs for losses of blood of less than 1,500 to 2,500 mL/70 kg. With greater losses, whole blood probably should be used. The concept that whole blood should be used for losses of blood greater than 2,500 mL/70 kg is now widely accepted, even in blood banking circles. In our hospital, patients undergoing operative procedures known to require more than 3 to 4 units of blood (e.g., aortoiliac reconstruction) are automatically crossmatched for whole blood instead of packed RBCs. The greater use of packed RBCs will allow blood banks to use the plasma to make other components of blood readily available. Depending on the type of surgery, anywhere from 50 to 80 percent of the RBCs given should be in the form of packed RBCs.

Because of this trend, some hospitals do not have whole blood readily available. This may force the surgical team to use packed RBCs for losses of blood greater than 1,000 to 1,500 mL/70 kg. One fear has been that if large volumes of packed RBCs reconstituted with a crystalloid are given, serum albumin deficiencies may result. On the basis of limited clinical data, Howland et al 132 proposed that infusion of saline-reconstituted RBCs would lead to low serum levels of fibrinogen and albumin, which could be an etiologic factor in postoperative pulmonary edema. This fear has not been substantiated. Despite this controversy, administration of saline-reconstituted RBCs for losses of blood less than 2,500 mL/70 kg usually does not induce low serum levels of albumin, although fibrinogen concentration can be decreased in the recipient. 133

The administration of packed RBCs is facilitated by reconstituting them with a crystalloid or colloid; however, not all crystalloids are suitable. If the solution contains calcium, clotting occurs. Therefore, lactated Ringer solution is usually not recommended for use as a diluent for packed RBCs (Table 46–14). Conversely, using flow rates and clot formation, Cull et al 134 found both lactated Ringer‘s solution and normal saline to be equally acceptable. A more important factor may be whether the diluent is hypotonic with respect to plasma. If so, then the RBCs will swell and eventually lyse. Those solutions that cause hemolysis are listed in Table 46–14. Clinicians who fear that the crystalloid-reconstituted RBCs may cause low serum concentrations may be tempted to use a plasma derivative, such as Plasmanate. 135 However, these solutions can cause hemolysis also. In the case of Plasmanate, its osmolality is only 180 mOsm/kg. Thus, those solutions recommended for reconstituted packed erythrocytes are 5 percent dextrose in 0.4 percent saline, 5 percent dextrose in 0.9 percent saline, 0.9 percent saline, and Normosol-R with a pH of 7.4.

Blood banks have made available packed RBCs that have been diluted with the addition of 100 mL of an adenine-saline-dextrose solution (Adsol) as described earlier. This addition allows the blood to flow readily without the addition of saline. If improved flow is desired, however, the clinician should not use 5 percent dextrose in water or lactated Ringer solution. 136 Also some centers have used modified whole blood (i.e., the platelets are removed but much more plasma remains than that with packed RBCs) in which the flow characteristics are similar to those of whole blood. 137

Leukocyte-Reduced Blood

The number of leukocytes in packed RBCs can be markedly reduced by three approaches. First, one can use an in-line filter that is integral to the collection system used to obtain blood from donors. Second, after collection, blood can be filtered through a filter attached to the collection bag. Third, the blood can be filtered immediately before or at transfusion.

Usually, leukocyte-reduced blood is used to minimize the likelihood of febrile, nonhemolytic transfusion reactions. However, it can be used to reduce alloimmunization and transfusion-transmitted infection.

Leukocyte-reduced blood will probably be used more frequently in the future. As indicated earlier, the Blood Products Advisory Committee of the FDA has recently recommended universal leukocyte reduction of cellular blood components. 125A This approach showed reduced infectivity, transfusion reactions, and immunosuppression.

Platelet Concentrates

Platelet concentrates are prepared by differential centrifugation, either from freshly drawn units of blood or from donors who specifically donate large amounts of platelets by recently developed plateletpheresis techniques. If platelets are stored at room temperature, they are satisfactory to use 5 days after collection with constant and gentle agitation. However, in the report of 10 septic platelet transfusions between 1982 and 1985, half were platelets stored for 5 days or more. A prospective analysis from 1987 to 1990 resulted in seven cases of sepsis in patients receiving platelets for thrombocytopenia secondary to bone marrow failure. 138 Because use of multidonor platelet products stored for 5 days results in an incidence of sepsis five times higher than use of those stored for 4 days, shorter storage times are being emphasized. In fact, platelet-related sepsis is about 1/12,000. 125A The increased risk of bacterial overgrowth is related to the storage temperature of 20 to 24°C. Because there is no test to identify bacterially contaminated blood products, any patient who develops a fever within 6 hours after receiving platelets, sepsis from platelets should be considered. If blood products are stored at 4°C, then they should not be used longer than 24 or possibly 48 hours after collection. The allowable storage time is based on *in vivo* survival. The longer allowable storage time at room temperature adds flexibility to the blood bank.

Indications for the use of platelets are somewhat difficult to define. The July 1989 FDA Drug Bulletin stated that platelets should not be given (1) to patients with immune thrombocytopenia purpura (unless there is life-threatening bleeding), (2) prophylactically with massive blood transfusion, (3) prophylactically after cardiopulmonary bypass. However, the use of fresh blood rather than platelet concentrates as a source of platelets is still emphasized by some cardiac groups 139 and is advocated by some for treatment of hemorrhage in general. 70, 71 More recently, the ASA Task Force 2 recommended that

1.
Prophylactic platelet transfusion is ineffective and rarely indicated when thrombocytopenia is due to increased platelet destruction (e.g., idiopathic thrombocytic purpura).
2.
Prophylactic platelet transfusion is rarely indicated in surgical patients with thrombocytopenia due to decreased platelet production when the platelet count is greater than 100 ¥ 109 /L and is usually indicated when the platelet count is below 50 ¥ 109 /L. The determination of whether patients with intermediate platelet counts (50–100 ¥ 1010 /L) require therapy should be based on the patient‘s risk of bleeding.
3.
Surgical and obstetric patients with microvascular bleeding usually require platelet transfusion if the platelet count is less than 50 ¥ 109 /L and rarely require therapy if it is greater than 100 ¥ 109 /L. With intermediate platelet counts (50–100 ¥ 109 /L), the determination should be based on the patient‘s risk for more significant bleeding.
4.
Vaginal deliveries or operative procedures ordinarily associated with insignificant blood loss may be undertaken in patients with platelet counts less than 50 ¥ 109 /L.
5.
Platelet transfusion may be indicated despite an apparently adequate platelet count if there is known platelet dysfunction and microvascular bleeding.

Patients with severe thrombocytopenia (<20,000 cells/ m3) and clinical signs of bleeding usually require platelet transfusion. However, patients may have very low platelet counts (much less than 20,000 cells/m3) and not have any clinical bleeding. Patients such as these probably do not need platelet transfusion. Individuals who have undergone trauma or require surgery need higher platelet counts. As indicated previously, these patients probably need a platelet count of 100,000 cells/m3 to maintain adequate hemostasis (see Table 46–5). Thus, both laboratory determinations and clinical evaluations must be taken into account before a decision to transfuse platelets is made.

TABLE 46–5. Correlation Between Platelet Count and Incidence of Bleeding

Whenever possible, ABO-compatible platelets should be used. The need to use them, however, is not well documented. Specific testing is difficult. Aggregation, the end point of RBC crossmatch, cannot be used because platelets cause clumping. The platelet membrane has immunoglobulins. Any additional deposit of recipient antibodies is difficult to detect. Despite the fact that platelets can be destroyed by antibodies directed against class I human leukocyte antigen proteins on their membranes and to a lesser extent by antibodies against ABO, platelets chosen for transfusion will continue to usually be chosen without regard to antigen systems. 140 ABO-incompatible platelets clearly produce very adequate hemostasis.

Platelets may be pooled into a single transfer bag or a syringe for administration or they may be administered as individual units. Several platelet administration sets are available for use. These all have filters with a pore size of about 170 m. Filters with smaller pore size (microaggregate filters) should not be used, because they tend to remove a significant number of platelets. Conversely, small filters are increasingly being used to hopefully decrease infectivity. Standard blood administration sets with 170-m filters are also acceptable. To decrease the loss of platelets, a 19-gauge needle, or greater, should be used. In order to ensure complete delivery of all the platelets available, the containers should be rinsed with saline.

The effectiveness of platelet transfusions is difficult to monitor. Under ideal circumstances, one platelet concentrate usually produces an increase of about 7,000 to 10,000 platelets/m3 1 hour after transfusion to the 70-kg adult. Thus, 10 units of platelet concentrates is required to increase the platelet count by 100,000 cells/m3 . However, many factors, including splenomegaly, previous sensitization, fever, sepsis, and active bleeding, may lead to decreased survivals and decreased recovery of transfused platelets.

In recent years, various different types of platelet concentrates have been proposed, including apheresis (i.e., collecting more platelets from one donor to avoid pooling of platelets from multiple donors), leukocyte-depleted platelets, and ultraviolet B-irradiated platelets. Whether these products will ultimately be used commonly is reviewed by Kruskall. 140

Fresh Frozen Plasma

FFP is prepared at the time that blood is obtained from a donor. It contains all the plasma proteins, particularly factors V and VIII, which gradually decline during the storage of blood. The use of FFP carries with it certain inherent risks that are observed with the use of essentially any blood product. The major risk is transmission of infectious diseases, such as hepatitis B, C, and AIDS. Other risks include sensitization to foreign proteins.

Despite all the problems associated with FFP, its use has increased tenfold during 1974 to 1984 and had reached almost 2 million units annually. This alarming increase caused the National Institutes of Health to conduct a Consensus Development Conference on Fresh Frozen Plasma in September 1984, of which I was a member. 53 More recently, the American Society of Anesthesiologists Task Force 2 recommended the administration of FFP with the following guidelines:

1.
For urgent reversal of warfarin therapy.
2.
For correction of known coagulation factor deficiencies for which specific correlates are unavailable.
3.
For correction of microvascular bleeding in the presence of increased (>1.5 times normal) prothrombin time or partial thromboplastin time.
4.
For correction of microvascular bleeding secondary to coagulation factor deficiency in patients transfused with more than one blood volume and when prothrombin time and partial thromboplastin time cannot be obtained in a timely fashion.
5.
FFP should be given in doses calculated to achieve a minimum of 30 percent of plasma factor concentration (usually achieved with administration of 10–15 mL/kg of FFP), except for urgent reversal of warfarin anticoagulation, for which 5 to 8 mL/kg of FFP usually suffice. Four to five platelet concentrates, one unit of single donor apheresis platelets, or one unit of whole blood provides a quantity of coagulation factors similar

to that contained on one unit of FFP (except for decreased, but still hemostatic, concentrations of factors V and VIII in whole blood).
6.
FFP is contraindicated for augmentation of plasma volume or albumin concentration.

As indicated in the section on coagulation problems with massive transfusions, they concluded that there is little scientific evidence to support the increasing use of FFP in clinical medicine. While FFP is a reliable solution for intravascular volume replacement in acute blood loss, alternative therapies are equally satisfactory and considerably safer. There is no documentation that FFP has a beneficial effect when used as part of transfusion management of patients with massive hemorrhage.
A further comment: The practice of administering both packed red cells and FFP to the same patient should be discouraged, as this adds to the cost and doubles the infection exposure. When conditions are appropriate, whole blood should be given.

The only indications for FFP administration they agreed on were the following:

1.
Replacement of isolated factor deficiencies (as documented by laboratory evidence)
2.
Reversal of warfarin effect
3.
In antithrombin III deficiency
4.
Treatment of immunodeficiencies
5.
Treatment of thrombotic thrombocytopenia purpura
6.
Massive blood transfusion (rarely, and only when factors V and VIII are <25% of normal)
7.
Requirements for indications 1 and 6 would be a prothrombin and partial thromboplastin time at least 1.5 times longer than normal.

Cryoprecipitate

Cryoprecipitate is prepared in such a way that it contains significant levels of factor VIII and fibrinogen. It also contains von Willebrand factor and fibronectin. All other plasma proteins are present in only trace amounts in cryoprecipitate. The use of cryoprecipitate in the treatment of factor VIII deficiency or hemophilia A has been outlined by Brown et al. 141 Cryoprecipitate contains factor VIII:C (the procoagulant activity), factor VIII:vWF (von Willebrand factor), fibrinogen, factor XIII, and fibronectin, which is a glycoprotein that may play a role in reticuloendothelial clearance of foreign particles and bacteria from the blood. Cryoprecipitate can also be used in the treatment of fibrinogen deficiencies and is preferable to commercially prepared fibrinogen preparations. This is because commercially prepared fibrinogen preparations have a very high incidence of hepatitis, whereas the risk of hepatitis in cryoprecipitate is no greater than that from a single unit of blood.

Cryoprecipitate is frequently administered as ABO compatible; however, this probably is not very important, because the concentration of antibodies in cryoprecipitate is extremely low. Cryoprecipitate may contain red cell fragments, and thus cryoprecipitate prepared from Rh-positive individuals can possibly sensitize Rh-negative individuals to the Rh 0 antigen.

“Paradoxical bleeding” has been described during infusion of cryoprecipitate. 142 This means that bleeding persists during infusion of cryoprecipitate despite factor VIII levels of 30 to 50 percent of normal, which should be adequate for hemostasis. Cryoprecipitate has a large amount of fibrinogen, so that if the hemophiliac is transfused with enough cryoprecipitate, serum fibrinogen levels may also rise, increasing the risk of bleeding, even in the presence of normal amounts of factor VIII. Conversely, hyperfibrinogenemia is not observed when commercial factor concentrates are used.

Cryoprecipitate should be administered through a filter and as rapidly as possible. The rate of administration should be at least 200 mL/h, and infusion should be completed within 6 hours of thawing.

Commercial concentrates of factor VIII have been the standard therapy for hemophilia. Although heat inactivation of factor VIII concentrate reduces infectivity, such a risk is still present. Recombinant DNA techniques have been used to develop factor VIII, which is free of disease transmission. 143 Mild cases of hemophilia may be treated without blood products by administration of DDAVP. Appropriate therapy is difficult to ascertain for patients who have inhibitors (alloantibodies) to factor VIII.

Fibrin glue is used occasionally by surgeons to create local hemostatis. It is prepared in a manner similar to that of cryoprecipitate. When FFP is thawed, the precipitate contains large amounts of fibrinogen. When centrifuged, about 4 mL of concentrated precipitate results. With added thrombin, it is applied locally, the efficacy of which is difficult to determine.

Prothrombin Complex

Factor IX can be recovered from plasma or plasma fractions by absorption with ion exchanges or inorganic chemicals. These products are all complexes of factors II, VII, IX, and X. Two commercial preparations available are Konyne (Cutter Laboratories, Berkeley, Calif) and Proplex (Hyland Division of Travenol Laboratories, Costa Mesa, Calif).

The main indication for this product is treatment of factor IX deficiency, or hemophilia B (Christmas disease). This is a hemorrhagic disorder that is distinguishable from hemophilia A only by laboratory tests. Factor IX or prothrombin complex has also been used for the treatment of acquired hypoprothrombinemic bleeding disorders, principally sodium warfarin overdose; however, its use is limited because of the risk of hepatitis.

Single-Donor Plasma

Single-donor plasma is plasma that has been removed from stored blood without any effort being made to preserve coagulation factors. Single-donor plasma is very effective as a volume expander. All the precautions outlined for the administration of FFP should be followed when single-donor plasma is administered. It obviously cannot be used to correct deficiencies in coagulation factors.

Other Options to Reduce Infectivity of FFP 143A

Solvent-Detergent

Plasma from multiple donors is pooled and subjected to a lipid-destroying mixture of a solvent (tri-*n*-butyl phosphate) and a detergent (Triton X-100) to inactivate lipid-enveloped infectious agents, including HIV, HTLV, hepatitis C virus, and hepatitis B virus. It has several disadvantages, including the risk of contamination of nonenveloped agents. Recalls can occur after any fraction of a lot has been released. It could be much more expensive.

Single-Donor Plasma, Donor Retested

A donation is made, and FFP is prepared. The unit (the first donation) is kept if all history and infectious diseases markers are negative. That unit is not released for use until the same donor donates a second unit at least 3 months after the first donation and again passes all donor intake and serologic testing. At that time, the first unit is released. The second unit is not released until the donor returns more than 3 months later for a third donation and again passes all the testing. At that time, the second unit can be released for use. This approach has obvious advantages but would be administratively complex.

Frequent-Donor Plasma

An inverse relationship exists between the number of donations a person has given and the chance that he or she will become seropositive. The relationship is independent of the time over which the donations were given. One appears to reach a maximum reduction of the incidence of seropositivity at four or more donations. Predictions are that reduction in seropositivity (and therefore transmission) to one-third to one-half the current figures is possible.

These options were presented at the University of California, San Francisco, Transfusion Committee meeting, and indicate that clinicians will have many ways of ensuring safer plasma for patients.

Summary

With the new tests of infectivity, the above FFP approaches may not be necessary.

Albumin and Plasma Protein Preparations

Several commercial products containing albumin are available for use as clinical volume expanders. Albumin is available as either a 5 or a 25 percent solution in isotonic saline. Furthermore, plasma protein fractions containing albumin and ?- and ?-globulins are available. These solutions are prepared commercially from albumin fractions from large pools of plasma reconstituted in isotonic electrolyte solutions. Such solutions can be given without regard to ABO blood type and without crossmatch and should be used primarily as volume expanders. They are very expensive and in short supply. In fact, bacterial sepsis has been associated with albumin administration. 144 For much of 1997, there was a shortage of 5 percent albumin because of the concern about contamination with Creutzfeldt-Jakob disease, or “mad-cow disease.” If available, albumin should be administered within 4 hours of initiation of the infusion because of potential contamination after entering the bottle.

Administration of plasma protein fraction solutions can result in hypotension, primarily as a result of a decrease in systemic vascular resistance 145 probably caused by the generation of bradykinin in recipients. 146 This type of prekallikrein activator activity rarely occurs with albumin. That administration of 5 percent albumin solution does not cause hypotension suggests that one of the globulin fractions in the plasma protein fraction is the cause.

We believe that administration of plasma protein fraction of 5 percent serum albumin solutions should be restricted for the treatment of documented hypoproteinemia or those conditions, such as burns and peritonitis, in which hypoproteinemia is likely. These solutions expand the vascular space for a longer period of time than balanced electrolyte solutions. 147 However, albumin‘s osmotic ability draws fluid into the vascular space from other extracellular fluid compartments. In most states of hypovolemia and dehydration, the entire extracellular fluid space already is depleted. Fluids such as 0.9 percent saline or lactated Ringer solution, which expand the entire extracellular fluid space, should be given.

The crystalloid versus colloid conflict has been debated for many years. The University Hospital Consortium developed guidelines for the use of albumin, nonprotein colloid, and colloid solutions. 148 Unfortunately, no anesthesiologists were represented in the Consensus Exercise. Their conclusions were not different from those described earlier.

Granulocyte Concentrates

Granulocyte concentrates have been obtained either by continuous-flow or intermittent-flow leukopheresis or by filtration leukopheresis. Such concentrates are difficult to obtain, require great time commitment on the part of the donor, survive for only short periods of time in the recipient, and have yet to be definitely proved efficacious in the treatment of recipients. In spite of these cautions, granulocyte transfusions are frequently used in larger centers for the treatment of severely leukopenic (a leukocyte count of 500/mm3) patients with evidence of septicemia and fever.

Granulocytes should be ABO- and Rh-compatible. Furthermore, many centers also check the recipient‘s serum for the presence of antibodies reacting against the donor white blood cells. Granulocytes should be administered through a filter and should be administered slowly over 2 to 4 hours because more rapid infusion may cause severe pulmonary reactions. Fever and chills are common after administration of granulocytes. Granulocyte concentrates should be administered daily for at least 4 to 5 days or until a satisfactory clinical response is observed.

ARTIFICIAL COLLOID SOLUTION THERAPY

The most commonly used artificial colloids are the dextrans, which are polysaccharides built up from glucose molecules. Dextran 70, with a molecular weight of about 70,000 (Macrodex), is an effective volume expander. 149 However, after infusion of more than 20 mL/kg/24 h, dextran 70 may interfere with normal blood clotting, causing a deficiency with crossmatching procedures and possibly causing bleeding diathesis.

These clotting defects are due to reduced platelet adhesiveness secondary to an antithrombin effect. Of prime importance is a significant incidence of severe anaphylactoid or anaphylactic reactions. 150, 151 These reactions are mediated by dextran-reactive antibodies that are IgG immunoglobulins. Dextran-reactive antibodies are formed in response to dextran polysaccharides. This process can be prevented if the potentially reactive sites on the dextranreactive antibody are blocked before the antibody is given. By prior administration of a hapten, a substance capable of combining with immunoglobulins but not producing a reaction, the reactive sites are occupied and unable to react to the antigen. Prior administration of dextran I (Promit, mo-lecular weight 1,000) has proved effective as a hapten, and decreases, but does not eliminate, the incidence of severe reactions. 152, 153 In addition, dextran 70 exerts a higher colloid osmotic pressure than blood. Thus, both dextran 70 and albumin may deplete the extracellular fluid space of water as does albumin. 154

Dextran 40, molecular weight of 40,000 (Rheomacrodex), has been used primarily to reduce blood viscosity and cellular aggregation and to improve microcirculation during low-flow states. It is often given prophylactically to decrease the incidence of postoperative thromboembolism. Blood viscosity may be increased by trauma, blood loss, burns, and endotoxin shock. Although viscosity can be decreased by dextran 40, the presumed improvement in flow through the microcirculation has not been well documented.

Expansion of the intravascular space by dextran 40 is of less duration and consistency than that observed with dextran 70. Carey et al 147 suggested that the addition of dextran 40 to crystalloid solutions with blood is beneficial for treatment of hypovolemia. Renal failure has been reported in several patients after administration of dextran 40 in an amount greater than 20 mL/kg. Obviously, with loss of blood greater than 20 percent of the blood volume, therapy with dextran 40 must be augmented with balanced electrolyte solution and blood.

Gelatin and starch preparations also have been produced to be used as intravascular volume expanders. 154 Although gelatin is the least effective, all of these synthetic products are as effective in expanding the intravascular volume as 5 percent albumin. However, they all can produce anaphylactoid reactions. 154

In addition to the dextrans, hydroxyethyl starch (Hespan) is frequently used in the United States. It is a synthetic starch molecule that resembles glycogen and is given as a 6 percent solution. Several studies have substantiated that Hespan is as effective as albumin as an intravascular volume expander. 155, 156, 157 The elimination of Hespan has not been completely resolved, although it is stored in the reticuloendothelial system of the liver for hours. Apart from its dilutional effect, it does decrease factor VIII when more than 1,000 mL/70 kg is given. 158 Although the precise dose required to cause a coagulopathy is not clear, a general recommendation is that no more than 20 mL/kg/day of 6 percent hetastarch be given. 159 Also, urinary specific gravity can be elevated when Hespan is given to patients with acute oliguric renal failure. 160 This emphasizes using urinary osmolality rather than specific gravity when Hespan is used. Finally, an additional problem was difficulty in interpretation of typing and antibody screening in samples that contained more than 30 percent of the hydroxyethyl starch solution. 161

Hypertonic Saline Possibly With Dextran

The sodium concentration of hypertonic saline solutions is 250 to 1,200 mEq/L. The theoretical advantage is that the greater the sodium concentration, the less total volume required for adequate resuscitation. The lower infusion volume is probably related to osmotically related movement of intracellular water into the extracellular space. Other mechanisms include a direct inotropic effect on the myocardium and a direct peripheral vasodilator effect. The main problem is severe hypernatremia, which can cause brain dehydration and can be fatal. The reader is referred to an excellent review by Moss and Gould 162 for further information.

Various hyperosmotic-hyperoncotic solutions have been used for resuscitation in hypovolemic patients. The most common combination is with hypertonic saline and 6 percent dextran 70. In animals, these fluids restore gut and kidney microcirculation more effectively than does normal saline. 163, 164, 165 Clinical practice will be required to ascertain the ultimate role, if any, of these fluids.

Synthetic Oxygen-Carrying Substances

Various substances that carry or facilitate the transport of oxygen have been made. The most notable is the perfluorochemical emulsion called Fluosol-DA. However, it will probably have little use because it carries oxygen (i.e., a small amount) only when the PaO2 is greater than 300 mm Hg. 165 Fluosol-DA was given to patients who had extensive surgical blood loss but who refused blood transfusions on religious grounds. In essence, administration of Fluosol-DA was of no benefit even in severe anemia. 166 Furthermore, there are many adverse effects. 167, 168 A newer perfluoro compound, perfluorocytylbromide, has been developed that carries three to four times more oxygen and has a longer half-life and presumably fewer problems than are associated with Fluosol-DA. Clinical trials will be required to determine its ultimate usefulness.

Hemoglobin can now be prepared from outdated human blood by a crystallization procedure and then dissolved in an isotonic medium. This solution can then be used as an intravascular volume expander. Animal studies indicate that this lysophilized crystalline solution is very effective. 169 However, these solutions are not without complications, 170 the most concerning of which are kidney toxicity and an increase in affinity for oxygen (i.e., left shift in the oxygen dissociation curve). A variety of approaches are being used, including crosslinking, pyridoxylation and polymerization, and conjugation and encapsulation, to decrease oxygen affinity, to decrease deposition in the reticuloendothelial system, and to increase half-life. Genetic engineering has provided hope for blood products. Initially, recombinant erythropoietin was developed for treatment of anemias and facilitation of autologous blood donation (Ch. 47). In 1992, a human recombinant hemoglobin was designed as a blood substitute. 171 By use of genetic engineering, it was made from *Escherichia coli.* It functions just like normal hemoglobin in terms of oxygen-carrying capacity, but it does not require crossmatching nor does it transmit disease or become rapidly outdated. How much recombinant material can be tolerated by humans remains to be determined.

As of 1998, several synthetic blood products are under investigation:

1.
Stroma-free hemoglobin solutions containing some modifications of the hemoglobin molecule
2.
Genetically engineered hemoglobin (e.g., having *E. coli* produce human red cells)
3.
Liposome-encapsulated hemoglobin solutions containing hemoglobin with a synthetic membrane
4.
Perfluorocarbons, organic solutions with high oxygen solubility

Autologous Transfusion
To prevent many of the complications seen with the use of synthetic blood products (e.g., renal damage, endotoxin release), various approaches have been used, such as cross-linking, polymerization, and conjugators with chemical or genetic engineering, as summarized earlier. With stroma-free hemoglobin, outdated human cells strip the oxygen-carrying substance out of the cell coating and then chemically modify it by one or more of the aforementioned approaches. By removing the cell lining, allergic reactions are prevented.

Originally, these products were viewed as blood substitutes. However, comparing safety is easy, but efficacy compared with that of bank blood is difficult to determine. FDA criteria of efficacy are difficult to establish. 172 Now, more emphasis is on their ability to transport oxygen. 173

Dietz has provided an excellent review of this entire topic. 174 Goodnough et al 143A have updated their status.
Patient Selection

The criteria for autologous donors are not as stringent as those for allogeneic donors. The Standards of the American Association of Blood Banks require that the donor-patient's hemoglobin (Hb) be no less than 11 g/dL or the hematocrit (HCT) 33 percent before each donation. 20 There are no age or weight limits. Patients weighing 50 kg or more may donate 450 ± 50 mL, in addition to testing samples, whereas those weighing less than 50 kg can donate proportionately smaller volumes. Donations may be scheduled more than once a week, but the last should occur no less than 72 hours before surgery to allow time for restoration of intravascular volume and for transport and testing of the donated blood. Donation is contraindicated when the patient has, or is being treated for, bacteremia or has a significant bacterial infection that can be associated with bacteremia. 20

Blood center and transfusion service policies differ regarding collection and use of autologous blood with positive viral markers. It is common practice to preclude use of blood reactive for hepatitis B surface antigen and the human immunodeficiency virus because of concerns for the safety of both patients and personnel. Some hospitals accept and transfuse autologous blood with any positive viral markers, and denying patients infected with human immunodeficiency virus the opportunity to receive their own blood could be a violation of the Americans with Disabilities Act. 21

Adolescents requiring corrective surgery for scoliosis are often ideal candidates for PABD. 22, 23 Experience is limited in very young children, but blood has been donated at the time of cardiac catheterization by children younger than 1 year who have weighed as little as 5 kg and were scheduled to undergo cardiac surgery. 24 Avoidance of allogeneic transfusion was reported in over 90 percent of children as young as 3 years who donated an average of three times before cardiac surgery. 25 Predonation of approximately 20 mL/kg has also been reported in children scheduled for general surgical procedures who ranged in age from 9 months to 10 years and weighed as little as 7.3 kg. 26 Factors limiting PABD by pediatric patients are commitment of parents, surgeons, and blood center personnel; patient cooperation; and vascular access.

There is extensive experience with PABD by older patients, especially those undergoing total joint arthroplasty 27, 28, 29, 30 and cardiac surgery. 31, 32, 33, 34, 35, 36, 37 Patients with unstable angina, left anterior descending coronary artery disease, congestive heart failure, or myocardial infarction within the previous 3 months are usually excluded. Critical aortic stenosis may be a contraindication, but one publication supports the safety of donation before aortic valve surgery. 38

Predonation by obstetric patients does not adversely affect the mother or the baby. 39, 40, 41, 42, 43 However, PABD can be justified only in patients with placenta previa. The need for peripartum transfusion cannot be predicted with sufficient accuracy to justify donation by other obstetric patients.

Patients scheduled for procedures during which transfusion is rarely necessary should be discouraged from donating. Approximately 50 percent of predonated units are not transfused to the donor-patient and are destroyed. 19 A survey of 600 hospitals in which 40 percent of predonated units were not transfused found that almost 25 percent were collected for procedures in which transfusion was only a remote possibility, and 40 percent of the patient-donors required no transfusions in the perioperative period. 16 Inappropriate donation by gynecologic surgery patients is especially common and can lead to inappropriate transfusion. A retrospective review of 263 patients having elective abdominal or vaginal hysterectomy demonstrated that PABD was the major risk factor for transfusion, independent of all other considered variables, including admission Hb level and estimated RBC loss. Twenty-five of 140 patients who predonated were transfused, whereas only one of 123 who did not was transfused. 44 It was concluded that the increased transfusion rate was most likely the result of iatrogenic anemia resulting from blood donation and a more liberal threshold for transfusing autologous blood.

Establishing a schedule of optimal preoperative collection of autologous blood, which is similar to a schedule for allogeneic maximum surgical blood ordering, can lead to more appropriate autologous blood collections. 45 The likelihood of a surgical patient requiring RBC transfusion can be predicted more accurately if, in addition to the type of surgical procedure, the patient‘s preoperative Hb value and weight are considered. 46 One group who calculated the predicted and tolerated blood loss for each surgical patient in order to determine the best transfusion strategy decreased wastage of autologous blood to less than 15 percent. 47

Erythropoietic Response to Donation

RBC production in autologous donors is dependent on adequate iron stores and is influenced by the number of units donated and the frequency of donation. Ferrous sulfate is usually prescribed in order to prevent anemia, allowing some patients to donate up to six units if donation is begun early. Twice-weekly phlebotomy is associated with greater erythropoiesis than is weekly donation. 37 Administration of recombinant human erythropoietin stimulates erythropoiesis and allows donation of more units. 48, 49, 50, 51 Patients with Hb levels of less than 13.5 g/dL appear to benefit most from administration of recombinant human erythropoietin. 51 Various dosage regimens have been reported, with the drug being administered subcutaneously or intravenously a few days to 3 weeks before surgery. The optimal dosage regimen for recombinant human erythropoietin has not been determined

Processing of Autologous Units

If CPDA-1 preservative is employed and blood is stored as liquid whole blood, the shelf life is 35 days. Separation into plasma and RBCs allows addition of a preservative solution (e.g., Adsol, Nutricel) to the RBCs, thereby extending the shelf life to 42 days. The plasma can be frozen or retained in the liquid state, but it is often discarded. Although RBCs can be frozen, the procedure is time consuming, expensive, and usually unnecessary. If surgery is delayed, liquid preserved RBCs can be frozen any time before 42 days.

Predonated units are conspicuously labeled as autologous, and the patient-donor's name and identifying number are written on the attached tag. Blood intended for autologous transfusion is tested for ABO type and Rh as a confirmation of patient identification. At this time, testing for infectious disease is not mandatory if blood is drawn and transfused at the same facility. However, most donations occur at blood centers, and the units are tested in the same manner as allogeneic blood. Testing of all units maximizes safety by allowing units with positive test results to be identified and tagged with biohazard labels or destroyed.

The issue of "crossover" of unused autologous units for allogeneic use is controversial. Although proponents argue that the blood supply could be increased, opponents point out that only about 30 percent of autologous units would be suitable for transfusion to other patients. 52 Units may be unsuitable on the basis of the donor's medical or risk behavior history and/or reactive test results. Blood centers may omit questions regarding risk behavior when obtaining autologous donor histories, precluding crossover of those units even if all test results are negative. When the questions are asked, there is a possibility that donors will not disclose disqualifying information because they assume the blood is only for their use. Thus, crossover of autologous units might result in transfusion of blood that is less safe than that from volunteer donors. Because many units are donated several days to weeks in advance of surgery and are reserved for the patient for a period of time after surgery, the potential shelf life for allogeneic use is short.

Complications of Donation and Transfusion

Autologous donors may sustain complications in association with the donation process or when the blood is transfused. Reaction rates among autologous donors of 1.5 to 5.5 percent 17, 53, 54 are similar to those in allogeneic donors. Most are transient vasovagal reactions requiring no treatment. As with allogeneic donors, younger donors experience more reactions than older donors. The reaction rate is highest among first-time donors and is greater in women than in men. In one series of approximately 187,000 allogeneic and 8,900 autologous donations, the reaction rate was 2.4 percent for allogeneic and 2.5 percent for autologous donors, whereas it was 13 percent in first-time donors. 55 AuBuchon and Popovsky 56 compared donors who did not meet allogeneic donor criteria (usually on the basis of cardiovascular disease) with those who met the criteria and found reaction rates of 4.3 percent and 2.7 percent, respectively. They were unable to identify any distinguishing features that were predictive of reactions. A review of approximately 4 million donor records found the prevalence of very severe outcomes (defined as events requiring hospitalization) to be 1 in 16,783 autologous donations and 1 in 198,119 allogeneic donations. 57

Three groups have reported experience with cardiovascular monitoring of autologous donors. Eighty-six percent of patients scheduled for coronary artery bypass grafting (CABG) evaluated with continuous electrocardiographic monitoring for 24 hours before and 24 hours after donation demonstrated at least one episode of ST-segment depression, but the incidence was not greater after donation. 58 In a similar study, 37 percent of patients had ischemic episodes during or after donation, and all indices of ischemia were more common on the day following donation. 59 A significant percentage of high-risk patients monitored during 224 donations exhibited hypotension, arrhythmias, ST-T wave changes, syncope, and tachycardia. 60 Five were treated with ephedrine and/or atropine, but it is unknown whether any morbidity would have occurred in the absence of treatment.

Although controversy regarding the advisability of PABD by patients scheduled for cardiac surgery continues, 61, 62, 63 several investigators have demonstrated its safety. 31, 32, 33, 34, 35, 36, 37, 38, 57, 58, 59 Donation of up to eight units by patients awaiting heart and lung transplantation has also been reported. 64, 65 Although PABD was without apparent adverse effects, even in patients receiving small doses of vasopressors, the authors 64, 65 caution that such donations are best performed in a hospital-based donor facility where full medical support is readily available.

The greatest potential hazard associated with transfusion of predonated blood is administration of an autologous unit to an unintended recipient. In an editorial, Linden and Kruskall 66 reviewed results of two surveys related to autologous transfusion. A 1992 American College of Pathologists survey found that autologous blood had been issued to the wrong patient on at least one occasion in the previous year by 0.9 percent of facilities and that almost half of those facilities reported that autologous units had been transfused to the wrong patient on one or more occasions. In a 1994 American Association of Blood Banks survey, 1.2 percent of respondents indicated errors involving transfusion of autologous blood to other patients during the previous year. Half of the errors occurred in institutions that permitted transfusion of units with positive viral markers.

A study of autologous donation error rates in Canada indicated that errors were associated with one of 149 autologous units. 67 About half of the errors involved late receipt of units or delivery of blood to the wrong hospital, but no data were presented to indicate whether the errors resulted in allogeneic transfusions. One unit of autologous fresh frozen plasma was transfused to the wrong patient. Errors were most frequent when components were produced and when shipment between hospitals or blood centers was involved.

An analysis of autologous donations by 175 pediatric orthopedic patients revealed 13 errors. 68 Three patients received allogeneic blood when autologous units were available. Several units expired, and some had to be destroyed because of difficulties related to storage, necessitating allogeneic transfusion. One patient received the wrong type of allogeneic blood. A prospective study by the Belgian SANGUIS group found that three of 55 patients with autologous blood available received allogeneic blood instead. 66

The clinician‘s index of suspicion for a transfusion reaction may be low when the patient is receiving blood thought to be his or her own, reducing the probability of early diagnosis and intervention and increasing the likelihood of serious consequences. In addition to hemolytic reactions due to inadvertent administration of the wrong unit of blood, there is potential for administration of contaminated blood. Two of 10 cases of sepsis due to transfusion of blood contaminated with *Yersinia enterocolitica* reported in the United States between 1991 and 1996 were associated with administration of autologous RBCs. 69 Additional reported complications are acute intravascular hemolysis resulting from transfusion of inadequately deglycerolized previously frozen RBCs 70 and hypotension, possibly resulting from hypersensitivity to stabilizers or sterilizing agents used in plastic blood bags. 71

Transfusion of Predonated Blood

The mere availability of autologous blood should not be an indication for transfusion. There is controversy regarding whether the indications for autologous and allogeneic transfusion should be the same. 72, 73 The “Practice Guidelines for Blood Component Therapy” of the American Society of Anesthesiologists 74 state that the indications for transfusion of autologous RBCs may be more liberal because of the lower (but still significant) risks associated with autologous blood. The “Guidelines for Red Blood Cell and Plasma Transfusion for Adults and Children” published by the Canadian Medical Association 75 state that the indications for transfusion of autologous and allogeneic blood should be the same.

Cost-Effectiveness of Predonation

The conventional measure of efficacy of PABD is the extent to which patients avoid allogeneic transfusion. Numerous studies have demonstrated attainment of that goal in about 70 percent of patients. 76 If avoidance of allogeneic transfusion is the only factor considered, PABD is efficacious. But is it cost-effective?

Charges for autologous units are usually more than those for allogeneic blood. The surcharge imposed by collecting facilities is based on personnel time required for scheduling and processing autologous donors and the complex logistics of handling and transporting the blood. One center estimated the direct costs of collecting, testing, and processing autologous and allogeneic blood to be $198.04 and $149.80, respectively. 77 Most units are drawn at blood centers and are subsequently shipped to, and purchased by, hospitals. Wastage rates of approximately 50 percent account for much of the expense of autologous blood because hospitals incur nonreimbursable costs for nontransfused units.

Decision analysis techniques have been applied to determinations of the cost-effectiveness of PABD. With this methodology, cost-effectiveness is expressed in dollars per quality-adjusted year of life saved (QALY).

Most accepted medical and surgical interventions cost less than $50,000 per QALY, a benchmark commonly applied as a threshold of cost-effectiveness. 78 Predonation for CABG costs $508,000 to $909,000 per QALY. 79 Estimates for primary unilateral hip replacement and unilateral knee replacement are $373,000 to $740,000 and $1,147,000 to $1,467,000, respectively. 80 For abdominal hysterectomy and transurethral resection of the prostate, the costs per QALY are $1,358,000 and $23,643,000, respectively. 77 Critics of QALY analysis point out that it includes only known, quantifiable risks and costs and uses death and dollars as the primary end points. 81 The peace of mind provided by PABD and additional potential benefits from avoiding risks of allogeneic transfusion other than currently identified infectious diseases cannot be measured.

Predonation practices must periodically be reviewed in light of changing surgical techniques and transfusion practices. For example, PABD has become standard practice for radical retropubic prostatectomy in some institutions, but some reports document decreasing transfusion requirements and question the need for predonation. 82, 83, 84 Not only was the recommendation for PABD eliminated at one institution, crossmatching was also discontinued and only a type-and-screen was routinely ordered. 83 After reviewing the records of 200 consecutive patients and the charges associated with PABD, another group concluded that PABD should be an option, but not a routine practice. 82

ACUTE NORMOVOLEMIC HEMODILUTION

Advantages

As with other autologous transfusion techniques, ANH is employed to reduce the need for allogeneic RBCs and to avoid the potential complications of transfusion. There are additional benefits of ANH that are not common to other autologous transfusion modalities. When the blood is kept in the same operating room with the patient, the chances of clerical error are eliminated. Unlike stored predonated autologous units, blood withdrawn during ANH does not undergo biochemical alterations associated with the “storage lesion.” Levels of 2,3-diphosphoglycerate are maintained, and there is no influence on the oxygen-Hb dissociation curve. 87 If the units are maintained at room temperature, platelet function is preserved, and hypothermia associated with transfusion of refrigerated blood is avoided. An additional potential advantage of ANH is improvement in tissue perfusion as a result of decreased viscosity.

There are also logistic advantages. 87 Scheduling difficulties may preclude the use of intraoperative blood recovery in urgent or emergent circumstances. The presence of malignancy or wound infection may contraindicate intraoperative blood recovery, but not ANH. It is simpler and less expensive to obtain autologous blood by ANH than by PABD. 88, 89 Patients with cardiovascular or neurologic disease may not be appropriate candidates for PABD but may safely undergo ANH while being intensively monitored in the operating room. When potential bacteremia (e.g., the presence of an indwelling urinary catheter or chronic osteomyelitis) precludes predonation, ANH may be the ideal solution. Because all of the blood is ordinarily reinfused in the operating room or shortly thereafter, the iatrogenic anemia and blood wastage often associated with PABD do not occur.

Efficacy

A decrease in allogeneic transfusion requirements of 20 to 90 percent has been reported for a wide variety of surgical procedures. 87, 90, 91, 92, 93, 94 However, early studies were flawed by the use of historic controls and did not consider the influence of increasing surgical experience or changing transfusion practices. Multiple blood conservation strategies were often employed, making the contribution of ANH difficult to evaluate. Transfusion criteria usually were not specified. The first prospective controlled study comparing ANH and PABD involved 50 patients undergoing radical retropubic prostatectomy performed by the same surgeon. The anesthetic technique was also standardized. The two autologous transfusion techniques were equally effective in decreasing the need for allogeneic transfusion. 95 In a larger nonrandomized study of 250 patients having radical retropubic prostatectomy, Monk et al 89 found the two techniques comparable in decreasing allogeneic transfusion and also demonstrated that ANH was more cost-effective than PABD.

Three small studies in which patients undergoing total hip or knee arthroplasty were randomized to a hemodilution or control group have been published. 96, 97, 98 Each study included only 30 to 40 patients, and the average volume of blood removed was about 1 L. One group reported that transfusion requirements were the same in both groups, 96 whereas a second group reported a decrease in the total number of

allogeneic units transfused in the ANH patients. 98 The third group of investigators, who also utilized PABD and intraoperative blood recovery, considered the technique successful because fewer patients in the ANH group required transfusion of their predonated units. 97

When employed during cardiac surgery, ANH is also referred to as *blood pooling* 99 or *intraoperative autologous donation.* 100 Most reported studies are retrospective. Schonberger et al 101 studied 100 patients undergoing CABG, 50 of whom had approximately 800 mL heparinized blood removed before cardiopulmonary bypass (CPB). They found that the net blood loss, amount of reinfused shed blood, and postoperative blood requirements were less in the ANH group. Sixty-five percent of ANH patients did not receive allogeneic blood, compared with 10 percent of control patients. Petry et al 99 retrospectively studied 90 patients having CABG, half of whom had heparinized blood (500–1000 mL) removed before CPB. Although 16 percent of control patients received no allogeneic blood, 44 percent of ANH patients did not require allogeneic transfusion. Canver et al 102 compared 140 patients who had a mean of 1,430 mL heparinized blood removed before CPB with 64 control patients in whom ANH was not performed. Although RBC transfusion requirements were no different, fewer units of platelets and fresh frozen plasma were administered to patients in whom ANH was performed.

In the first of two prospective studies, Helm et al 100 randomized 90 patients undergoing CABG or valvular operations to have ANH performed or to serve as controls. An average of 1,540 ± 302 mL was removed before anticoagulation in the treatment group. Uniform transfusion criteria were applied. The investigators found a significant decrease in both the percentage of patients who received allogeneic RBCs (17 versus 52%) and the number of RBC units transfused per patient (0.28 ± 0.66 versus 1.14 ± 1.19 units) in the ANH group. There was no difference in chest tube output, incidence of excessive postoperative bleeding, or coagulation factor transfusion requirements. In a second prospective study, 100 patients undergoing CABG were randomized to have 10 mL/kg heparinized blood withdrawn before CPB or to serve as controls. 103 Transfusion indications were standardized. Patients in the ANH group had a 28 percent reduction in chest tube drainage at 8 hours and a 45 percent reduction in total allogeneic units transfused. Fifty-two percent of ANH patients received no transfusion, whereas 31 percent of control patients were not transfused.

Mathematic and computer modeling have been used to assess the efficacy of ANH. 104, 105, 106 Results are somewhat conflicting, but several of the conclusions are reasonable. First, the RBC “savings” depends on the patient‘s initial HCT value, the volume of blood removed, and the blood loss. 105 Second, the amount of RBCs saved is overestimated by the simple formula conventionally utilized for ANH. 104 Most importantly, efficacy is greatest when substantial hemodilution is followed by significant blood loss. For example, a savings of four units of allogeneic transfusion can be realized when a patient with an estimated blood volume of 5 L and HCT of 45 percent is hemodiluted to a HCT of 15 percent. If only two units are removed, resulting in a HCT of approximately 37 percent, only about 100 mL is saved. 106

Hemodilution is efficacious in reducing RBC transfusion requirements in patients undergoing cardiac surgery, but the potential advantage of fresh whole autologous blood in decreasing postoperative bleeding remains to be proved. There are limited data from controlled studies to document the efficacy of ANH in other surgical populations.

Physiologic Effects

The withdrawal of blood and its replacement with acellular fluid are accompanied by a decrease in arterial oxygen content, but oxygen delivery is usually unaffected. A number of mechanisms are invoked as physiologic compensation for the acute reduction in Hb. The most important is an increase in cardiac output. The primary factor responsible for the increased cardiac output seen with ANH is decreased viscosity. The decrease in viscosity is most pronounced between HCT values of 45 and 30 percent, and the effect is progressively less significant when the HCT is below 25 percent. 107 Decreased viscosity results in increased venous return, decreased peripheral resistance, and reduced afterload. The reduced peripheral resistance may also be due to reflex vasodilation or local regulatory factors, such as endogenous release of nitric oxide. 108 In the canine model, there is evidence of increased myocardial contractility, in addition to decreased afterload, as a contributing factor to the increased cardiac output. 109 Increased sympathetic stimulation of the heart may also contribute. 107

The relative importance of an increase in heart rate or stroke volume to the increased cardiac output depends on the species studied, the subject‘s state of awareness (i.e., awake versus anesthetized), and the type of anesthesia administered. In the anesthetized adult, an increase in stroke volume is most important;

heart rate does not ordinarily increase in the absence of hypovolemia. Anesthetized children tend to respond with tachycardia, as do awake dogs. An increase in heart rate occurs in awake baboons, whereas stroke volume increases during ANH in anesthetized baboons. 107

Although increases in total and local blood flow are sufficient to maintain oxygenation in resting normovolemic, moderately hemodiluted subjects, other mechanisms are involved with more extreme degrees of ANH. These include redistribution of blood flow to the heart and brain and increased tissue oxygen extraction. A significant increase in coronary and myocardial blood flow occurs with ANH in subjects with normal coronary circulation. Coronary vasodilation and decreased viscous resistance are responsible for the increased coronary blood flow. Myocardial blood flow and arterial oxygen delivery are maintained at HCT values as low as 12 percent in dogs and 9 percent in pigs. The myocardial oxygen extraction ratio remains unchanged in baboons and pigs hemodiluted to HCT values of 4 percent and 9 percent, respectively. Redistribution of myocardial blood flow away from the subendocardium is observed at HCT levels of approximately 9 percent, signifying exhaustion of the subendocardial vasodilator capacity and thus the limit of tolerance to hemodilution. 107 The limits of ANH have been studied in a canine model of coronary artery disease. 110 The median lowest Hb level tolerated without contractile dysfunction in animals with surgically induced stenosis of the left anterior descending coronary artery was 7.5 g/dL. Marked contractile dysfunction was seen at a mean Hb level of 6.0 ± 0.4 g/dL. Increasing the Hb level by approximately 2 g/dL restored contractile function. The cardiovascular compensatory mechanisms remained intact for at least 4 hours. 111

Patient Selection

Hemodilution should be considered for any patient with an adequate Hb who is expected to lose more than 25 percent of estimated blood volume. Because the Hb decreases approximately 1 g/dL for each unit of blood removed and because ANH is not efficacious if only a small volume of blood is withdrawn, it usually is inappropriate to employ the technique when the Hb is less than 11 g/dL, particularly if limited ANH is to be performed.

Although some anesthesiologists limit use of the technique to healthy adults, ANH has been employed in small children 112, 113, 114, 115, 116, 117, 118, 119 and the elderly. 120, 121, 122, 123 Two groups of investigators have studied the tolerance of patients with known coronary artery disease to acute limited hemodilution. Catoire et al 122 employed transesophageal echocardiography in patients undergoing abdominal aortic surgery who were hemodiluted to a target HCT of 30 percent and a comparable group who were not hemodiluted. Hemodynamic changes associated with aortic clamping were less marked in the ANH group. The authors concluded that ANH did not worsen myocardial ischemia and may actually improve hemodynamic tolerance to aortic clamping. Herregods et al 124 studied patients with left main coronary artery stenosis undergoing semiurgent CABG who were hemodiluted to HCT levels of 34 percent and patients with similar lesions in whom ANH was not performed. They found no increase in frequency, degree, or duration of ST-segment changes in the ANH group. Allogeneic transfusion requirements were decreased by ANH: 64 percent of treated patients did not require allogeneic blood, compared with 38 percent of control patients.

The patient‘s overall health status, rather than chronologic age should be considered. In a group of patients aged 66 to 88 years (mean, 76 ± 2 years), Spahn et al 123 demonstrated that ANH to a mean Hb of 8.8 ± 0.3 g/dL was well tolerated. In a separate study, the investigators hemodiluted patients receiving chronic ?-adrenergic blocker therapy to Hb levels of 9.9 ± 0.2 g/dL before CABG was performed. The patients tolerated ANH well, and it was concluded that compensatory mechanisms during ANH are largely independent of age and left ventricular ejection fraction. 125

Experience with extreme ANH in children and adolescents has been reported by several groups. Fontana et al 118 demonstrated that global oxygen consumption was maintained in healthy children hemodiluted to a mean Hb level of 3.0 ± 0.8 g/dL. The oxygen extraction ratio increased from 17 to 44 percent, and mixed venous oxygen saturation decreased from 90.8 ± 5.4 to 72.3 ± 7.8 percent. In children of the Jehovah‘s Witness faith in whom the HCT was reduced to 16 percent, the oxygen extraction ratio increased from 22 to 33 percent, and mixed venous oxygen saturation declined from 80 to 70 percent. 115 Aly Hassan et al 117 also demonstrated that global tissue oxygenation was preserved at HCT levels of approximately 17 percent. The safety of extreme ANH to HCT values of 12 to 14 percent in combination with mild hypothermia and

controlled hypotension to mean arterial pressures of 40 to 50 mm Hg has been shown in patients undergoing spinal fusions. 116

Contraindications

Patients with decreased renal function are not suitable candidates for ANH because excretion of diluent fluids may be impaired. Significant restrictive or obstructive pulmonary disease is a contraindication because decreased arterial oxygen content is inherent with ANH and tissue oxygenation may be inadequate. Preexisting coagulopathy precludes the use of the technique. Caution is required in patients with hepatic disease or other disorders associated with a reduction in coagulation factors, thrombocytopenia, or impaired platelet function.

Technique

The amount of blood to be withdrawn depends on the patient's estimated blood volume (EBV), preoperative HCT, and the lowest HCT desired. 126 The volume (V) to be removed equals the EBV multiplied by the patient's initial HCT (Ho) minus the minimum allowable HCT (Hf), divided by the average HCT (Hav):

V = EBV ¥ [(Ho) – (Hf)]/Hav

For a patient with an EBV of 5 L, an HCT of 45 percent, and a desired lower HCT of 30 percent, the approximate amount of blood to withdraw is calculated as

V = 5 L ¥ [45 – 30]/37.5 = 2,000 mL

Serial HCT determinations should be performed during blood removal and at intervals throughout the surgical procedure.

Hemodilution is usually performed in the operating room following induction of anesthesia. If an induction room or holding area is adequately equipped with monitoring equipment, it may be advantageous in terms of efficiency of operating room utilization to perform ANH in such an area. The procedure can also be initiated before induction of anesthesia. Atallah et al 127 compared the stress response to ANH performed before and after induction. On the basis of hemodynamic, hematologic, biochemical, and hormonal indexes, the investigators concluded that ANH is not a stress-producing technique and can be performed in awake or anesthetized patients.

Crystalloid and/or colloid are infused as blood is withdrawn. When crystalloid is used, the amount must be approximately three times the volume of blood removed because much of the crystalloid moves out of the intravascular compartment. Colloids have the primary advantage of intravascular retention. Therefore, the amount infused can be approximately equal to the amount of blood removed. Some evidence suggests that when albumin is used as a diluent, the volume may need to be greater than the volume of blood removed to ensure normovolemia. 128 Hemodynamic studies comparing dextran, albumin, and hydroxyethyl starch have demonstrated no significant differences among diluents. 129 The advantage of crystalloid, in addition to cost, is that excess fluid can easily be excreted if a diuretic such as furosemide is administered before reinfusion of the blood.

Blood is withdrawn from a central or large peripheral vein or radial artery. Use of veins distal to the antecubital area is not recommended, because poor blood flow often results in clotting. When an artery is used, blood pressure can be transduced intermittently by incorporation of a stopcock in the system. Blood is collected in standard blood bags containing anticoagulant, usually citrate-phosphate-dextrose. Hemodilution kits containing bags with an anticoagulant, a Y-type connection set with Luer-Lok adapter, and a blood recipient identification band are available (Autologous Blood Collection Kit 4R5012, Fenwal Division, Baxter Healthcare, Deerfield, Ill.). In cardiac surgery, heparinized blood can be collected from the venous line into transfer bags, or an autologous kit can be used (Autologous Blood Collection Kit 4R5010, Fenwal Division, Baxter Healthcare, Deerfield, Ill.). A scale should be used to weigh the bags to ensure that they contain the appropriate amount of blood relative to anticoagulant. Ideally, an automated blood collection and mixing device or blood "shaker" is used to monitor collection volumes and prevent clotting (Blood Shaker/Flow and Weight Monitor Model 1040, Sebra, Tucson, Ariz.).

Monitoring requirements depend on the patient's physical status, the operative procedure and anticipated blood loss, and the degree of hemodilution. Use of a pulmonary artery catheter during extreme ANH is advisable to permit determination of mixed venous oxygen saturation as a measure of global oxygenation. Preliminary data utilizing a synthetic perfluorochemical temporary oxygen carrier during ANH indicate that it increases mixed venous oxygen tension. 130 It may be possible to increase the number of units withdrawn by using a temporary oxygen carrier to provide an additional margin of safety.

Each unit is labeled with the patient's name, hospital number, and time of blood withdrawal and is numbered sequentially. The blood is kept in the same operating room as the patient and is maintained at room temperature to preserve platelet function. If it is anticipated that more than 8 hours will elapse before reinfusion, refrigeration of the blood is required. Refrigerated units must be reinfused within 24 hours or be discarded. 20 Blood is reinfused after major blood loss has ceased, or sooner if indicated. The units are reinfused in the reverse order of collection so that the first unit, which has the highest HCT and the most clotting factors, is administered last. Estimation of blood loss and serial HCT determinations are used to guide transfusion therapy.

Complications

The minimal safe HCT depends on the patient's ability to compensate for the decreased arterial oxygen content. Myocardial ischemia and cerebral hypoxia are the major potential complications. The augmented cardiac output increases myocardial oxygen consumption while the oxygen content of blood supplying the myocardium is reduced. Tachycardia and decreased cardiac output resulting from hypovolemia can further impair myocardial oxygen supply-demand relationships. In the adult, tachycardia should be considered an indication of hypovolemia and should be corrected immediately.

Laboratory studies of the effects of extreme ANH on the intestine indicate that jejunal mucosal oxygen supply is well maintained at HCT values of 10 percent. 131 In the canine model, myocardium compromised by coronary stenosis is more sensitive to hemodilution-induced ischemia than is normally perfused gut mucosa. 132 These findings limit the potential usefulness of gastric tonometry as a guide to tolerable levels of hemodilution.

Animal studies indicate that cerebral function may not be affected until the HCT is less than 5 to 10 percent. 133, 134 In the canine model, hemodilution to a HCT of 19 percent impairs hypocapnia-induced vasoconstriction in the brain and spinal cord. 135 A potential clinical implication is that induced hypocapnia might be a less effective maneuver to reduce increased intracranial pressure during ANH. Conversely, the blunted vascular response to hypocapnia may confer brain protection by maintaining cerebral blood flow in the presence of decreased oxygen-carrying capacity. Experience with children hemodiluted to Hb levels of approximately 3 g/dL demonstrates the safety of extreme ANH in young patients without cerebrovascular disease. 118 Hemodilution to Hb levels of 7 to 9 g/dL in elderly patients, some of whom would be expected to have cerebrovascular disease, has not been reported to result in neurologic dysfunction. 122, 123 However, no studies have specifically addressed the issue, and caution is advised in patients with carotid or vertebral artery disease.

Coagulopathy related to dilution of clotting factors and increased bleeding resulting from enhanced capillary blood flow are potential complications. However, pediatric patients subjected to a 75 percent volume exchange during ANH still had a mean platelet count of 158 ± 26 ¥ 109 /L, which is ordinarily adequate for hemostasis. 119 Monitoring coagulation parameters is advisable with extreme ANH but is not required during moderate ANH.

Peripheral edema is common in hemodiluted patients, especially when crystalloid is administered as the sole diluent. However, pulmonary edema should not occur if ANH is properly performed.

Semicontinuous Flow Centrifugation Devices

Several devices are available. The degree of automation, size, cost, and clinical applications vary. The disposable equipment consists of an anticoagulation and aspiration assembly, a reservoir with filter, a centrifuge bowl, a waste bag, and tubing (Fig. 47–3). The double-lumen aspiration set incorporates an anticoagulant line through which either a heparin or a citrate solution is administered at a controlled rate. Recovered blood, mixed with anticoagulant, is collected in the disposable reservoir containing a filter. The

filtered blood is then pumped into a wash bowl with a centrifugation speed of approximately 5,000 repetitions per minute. Once the bowl is filled, the contents are washed with saline. The RBCs suspended in saline are pumped into a reinfusion bag. Most of the white blood cells, platelets, activated clotting factors, plasma Hb, cell fragments, and other debris are eliminated into the waste bag along with excess saline wash solution. The washing and concentrating process requires 3 to 10 minutes, depending on the device.

Characteristics of Processed Blood

The HCT of processed blood is 50 to 60 percent and can be varied by altering the processing parameters. The oxygen transport properties and survival of recovered RBCs are equal or superior to those of stored allogeneic RBCs. The 2,3-diphosphoglycerate content of recovered blood has been measured as a marker of RBC function. Processed blood consistently has higher 2,3-diphosphoglycerate levels than allogeneic blood. 136, 137, 138 The survival of RBCs has been studied by use of51 Cr-tagged cells recovered during spine, 139 aortic, 137, 140, 141 and cardiac 142 surgery. The life span is comparable to that of transfused allogeneic RBCs. The pH of processed blood is alkaline, and potassium and sodium levels are normal. 138

Plasma Hb levels may exceed 400 mg/dL in blood recovered during cardiac surgery and may be several times higher in orthopedic surgery. Adequate washing removes over 90 percent of the free Hb. 143 Residual leukocytes and platelets are present in washed blood, but their function and significance are uncertain. 144 Tumor necrosis factor-?, a cytokine produced by stimulated monocytes that has immunomodulatory activity, has been detected in unwashed, recovered blood. 145 Plasma elastase, an enzyme implicated in the pathogenesis of respiratory distress syndrome, has also been demonstrated in unprocessed blood. Washing removes these substances, thereby reducing the potential deleterious effects associated with reinfusion of unprocessed blood. 146

When citrate is used as an anticoagulant, it is metabolized by the liver. Processed RBCs do not contain a clinically significant amount of residual heparin. 143, 147, 148 Instruments conventionally employed in cardiac surgery for determining activated clotting time and heparin assays (e.g., Hepcon, Medtronic Blood Management, Parker, Col.) cannot be used to measure residual heparin because coagulation proteins and antithrombin III, which are required for the test, are removed during the wash cycle. 143, 149

Catecholamines are not removed during processing, and significant hypertension has been reported when blood recovered during surgery for pheochromocytoma was reinfused. 150 Washing does remove tissue factor in blood contaminated with amniotic fluid. 151 D-dimer levels have been measured in recovered blood as an indication of activation of the coagulation and fibrinolytic systems and the presence of fibrin degradation products. Although D-dimer levels may be increased 85 times in unwashed blood, normal levels are found in processed blood. 152

Reports describing the quality of blood processed with newer devices employing technology different from semicontinuous flow centrifugation are beginning to appear. 153, 154, 155, 156 Unacceptable residual heparin levels were demonstrated with one ultrafiltration device. 153 Initial reports indicate that the continuous autologous transfusion system (CATS, Fresenius AG, Bad Homburg, Germany) produces a product with a mean HCT of 62 percent, greater than 99 percent heparin elimination, and removal of most plasma proteins. 154 An *in vitro* study using soya oil, which has a fatty acid composition similar to that of fat found in bone marrow, indicated complete removal of fat particles. 155

Complications

Potential complications associated with use of cell processing devices include air and fat embolism, pulmonary dysfunction secondary to infusion of debris in recovered blood, coagulopathy, renal dysfunction, sepsis, and dissemination of malignant cells. The most serious complication—air embolism—is rare if the devices are used in accordance with the manufacturer‘s instructions. However, one report cited an incidence of fatal air embolism of 1:30,000 to 1:38,000 in approximately 127,000 blood recovery procedures. 157 All cases involved infusion of recovered blood under pressure. Contributing causes were deviations from accepted practice, lack of operator vigilance, and insufficient knowledge of the procedure. Suggested measures to prevent air embolism include transferring the blood to a reinfusion bag before transfusion (i.e., not reinfusing directly from the recovery container) and avoiding reinfusion under pressure.

Although processed blood, particularly that collected during orthopedic procedures, contains visible fat particles, there is no documented instance of fat embolism associated with the technique. There are also concerns about transfusing blood containing leukocytes, platelets, and other cellular debris that can lodge in the lungs, potentially causing pulmonary dysfunction. Despite reinfusion of shed blood in thousands of patients, no adverse effects on pulmonary function have been documented.

Lysis of RBCs can occur as a result of high vacuum suction levels or aspiration techniques that cause turbulence during blood collection. Two cases of renal dysfunction requiring dialysis have been reported. 158 In both cases, excessive vacuum levels and insufficient washing of recovered blood were implicated. Most operator‘s manuals recommend a maximum vacuum level of 100 to 150 mm Hg. A laboratory study demonstrated the absence of excessive hemolysis when levels of up to 300 mm Hg were employed, but the author stressed that the lowest level of vacuum compatible with a clear surgical field should be used. 159 Use of a suction regulator with a factory-set maximum vacuum level is recommended, and the accuracy of the suction regulator should periodically be verified. 158 Suctioning small amounts of blood mixed with air (skimming) may induce greater degrees of hemolysis than high suction vacuum levels. 159 This is most likely to occur during orthopedic surgery. Greater wash volumes are usually recommended during orthopedic surgery. In any case, the blood should be washed until the effluent is clear.

Processed blood is depleted of coagulation proteins and functional platelets. It is not surprising that coagulopathy has been reported in patients receiving more than 15 units of processed blood. 160 The same guidelines for platelet and fresh frozen plasma administration apply when shed blood and allogeneic RBCs are infused. 74 There is a report of two cases of disseminated intravascular coagulation in patients undergoing spine surgery during which recovered blood was reinfused. 161 By the authors‘ own admission, vacuum levels of 300 mm Hg were used throughout the procedure. Coagulopathy may have been the fault of the procedure, but it is more likely that a faulty procedure caused the coagulopathy.

As a general principle, blood contaminated with intestinal contents should not be reinfused. However, there are reports of intraoperative blood recovery and reinfusion in patients with blunt and penetrating abdominal injuries associated with disruption of bowel integrity. 162, 163 One report evaluated trauma patients who received potentially culturepositive blood. 164 Wound infection rates were identical to those in patients with similar injuries who were not autotransfused. *In vitro* studies demonstrate that cell washing reduces the bacterial count but does not remove all bacteria. 165 The risk-benefit ratio of employing the technique when the wound is contaminated (or potentially contaminated) with intestinal contents should be carefully evaluated.

Bacteriologic and endotoxin analysis of blood recovered during cardiac surgery has shown a significant incidence of bacterial contamination with gram-positive commensals of the skin, as well as low concentrations of endotoxin. No adverse clinical outcomes were noted. 166, 167 Similar results have been found with blood recovery during liver transplantation. 168 It is speculated that the sources of contamination are the skin and room air and that the quantity of bacteria is too small to be of clinical significance in patients receiving prophylactic antibiotics. This hypothesis is supported by a study in which blood recovered during hip arthroplasty in patients receiving antibiotic prophylaxis with cefuroxime was compared with blood from patients not receiving antibiotics. 169

The presence of tumor cells in the operative field has traditionally been considered a relative contraindication to intraoperative blood recovery. Although experience with the technique in patients with genitourinary tumors undergoing radical cystectomy, nephrectomy, prostatectomy, and radical hysterectomy indicates that it may be acceptable, 170, 171, 172 laboratory studies using human tumor cell lines have demonstrated that tumor cells remain in the washed RBC suspension. 173, 174 Filtration of the RBC concentrate with a third-generation leukocyte-reduction filter removes the tumor cells. 175, 176, 177, 178

An additional safety issue when blood is recovered during urologic procedures is contamination of the surgical field with urine. Biochemical analysis of concentrated RBCs mixed with an equal volume of urine has demonstrated complete removal of urine constituents. 176 Concentrated RBCs inoculated with bacteria demonstrated bacterial growth, indicating that bacteria were not removed by the washing process. The investigators suggested preoperative elimination of bacterial urinary tract infection when blood recovery is planned in patients undergoing urologic surgery. 176

Blood should not be aspirated during application of topical hemostatic agents, such as thrombin and microfibrillar collagen hemostat (Avitene). *In vitro* studies indicate that it can pass through the filtering system and become lodged in tissues. 179 Laboratory investigations have demonstrated that either a leukocyte-reduction filter or a 20-?m microaggregate filter can remove approximately 97 percent of potentially thrombogenic particles of Avitene. 180 Blood also should not be aspirated when the wound is irrigated with antibiotics that are not licensed for parenteral use or during the application of methylmethacrylate. The wound should be copiously irrigated following use of these substances before blood recovery is resumed.

Clinical Applications

Intraoperative blood recovery should be considered when it is anticipated that blood will be shed into a clean wound from which it can be aspirated without undue hemolysis. Limiting use of the procedure to situations in which the following criteria are met can serve as a guideline: blood would normally be crossmatched, the anticipated blood loss is at least 20 percent of the patient's estimated blood volume, 10 percent or more of patients undergoing the procedure require transfusion, the mean transfusion for the procedure is more than one unit. The major applications are cardiac, 181, 182, 183, 184 vascular, 137, 140, 185, 186 orthopedic, 187, 188, 189, 190, 191 and trauma surgery 162, 163, 164, 165, 192, 193 and liver transplantation. 194, 195

Utilization appears to be increasing in neurosurgery. Following the tradition of Harvey Cushing, 5 the Mayo Clinic group reported experience with blood recovery during resection of intracranial arteriovenous malformations. 196 More recently, Cataldi et al 197 infused recovered blood in patients undergoing intracranial surgery, and Jimenez and Barone 198 demonstrated a 46 percent decrease in allogeneic transfusion requirements with intraoperative blood recovery in children undergoing surgery for craniosynostosis.

Preliminary clinical data indicate that the technique can safely be utilized during cesarean delivery if a separate suction apparatus is used for removing the amniotic fluid. 199 Laboratory studies confirming removal of tissue factor in aspirated blood that contains amniotic fluid also suggest that the technique can be utilized after delivery of the baby when unexpected hemorrhage occurs. 151

Cost-Effectiveness

The expenses associated with cell processing units include not only the apparatus and the software but also the time of a dedicated, trained operator. The institution's experience with allogeneic transfusion for comparable procedures should be periodically reviewed when the procedures for which the technique will be used are determined.

Three groups of investigators studied patients undergoing primary total hip replacements and concluded that intraoperative blood recovery was not cost-effective and was unnecessary in patients who donated two or three units before surgery. 189, 190, 200 Siller et al 201 compared the efficacy and the cost of PABD and intraoperative blood recovery in adolescents undergoing posterior spinal instrumentation and fusion. The cost of intraoperative blood recovery was approximately $240, and patients were billed approximately $640. The addition of intraoperative blood recovery had no effect on blood exposure, and the investigators do not recommend it if sufficient predonated blood is available.

After reviewing their experience with blood recovery during emergency spine surgery, Cavallieri et al 192 suggested that cost-effectiveness could be improved if use of the technique was restricted to patients with thoracolumbar spine injury with preoperative HCT values of less than 35 percent and Injury Severity Scores of greater than 20. Smith et al 193 calculated the total cost of intraoperative blood recovery for patients sustaining abdominal trauma to be $63,252, whereas the cost of bank blood would have been $114,523. Use of the technique was considered cost-effective in 75 percent of the cases.

Two groups evaluated cost-effectiveness of intraoperative autologous transfusion during abdominal aortic surgery. Using $50,000/QALY as a threshold, Huber et al 185 concluded it was not cost-effective. The cost was $263.75 per case, or $120,794/QALY. They recommended the technique be restricted to select cases in which large volumes of blood loss are anticipated. Goodnough et al 186 calculated that the RBC volume recovered represented the equivalent of 1.6 allogeneic RBC units. The mean blood bank cost saved by use

of the device was $248, or 79 percent of the $315 spent on use of the technique. There was no decrease in the percentage of patients transfused unless recovered volumes infused exceeded 750 mL.

Although intraoperative blood recovery is not cost-effective for most patients undergoing primary total joint replacements, it may be for those having hip arthroplasty revisions. For intra-abdominal aortic surgery, spine, and abdominal trauma procedures, it is often reasonable to use an anticoagulant-suction apparatus and blood collection reservoir but not to open a centrifuge bowl unless sufficient blood is collected to make processing worthwhile.

Unprocessed Blood

The primary stimulus for developing devices that do not require processing of recovered blood was the desire to eliminate the need for expensive equipment that required the constant attention of dedicated operators. Intraoperative use is usually restricted to vascular surgery. The devices are more commonly used in the postoperative period

Cardiac Surgery

Blood within the mediastinum undergoes coagulation and subsequent fibrinolysis. It contains virtually no fibrinogen, and no anticoagulation is required before reinfusion. The HCT value usually ranges from 20 to 25 percent, and free Hb levels are 300 to 400 mg/dL. 143, 202, 203, 204, 205 The transfused RBCs have normal survival 206 and oxygen delivery capacity. 207

Fibrin degradation products are detected in most patients when unwashed shed mediastinal blood is reinfused. 208, 209, 210 The presence of fibrin degradation products should not be interpreted as indicative of disseminated intravascular coagulation in the absence of clinical bleeding. The greatest danger posed by the fibrin degradation products is misinterpretation of laboratory tests for disseminated intravascular coagulation and unnecessary blood component administration. 208 Serum creatine kinase, serum glutamic-oxaloacetic transaminase (SGOT), and lactate dehydrogenase levels are also elevated after reinfusion of unwashed mediastinal blood. 211, 212, 213, 214, 215 Conflicting results have been reported regarding elevation of the MB band of creatine kinase. Caution must be exercised when cardiac enzyme levels in patients who receive shed mediastinal blood are interpreted. The enzyme elevations caused by reinfused blood can mimic a myocardial infarction. Alternatively, falsely attributing enzyme abnormalities to the shed blood may result in a myocardial infarction going undiagnosed.

The cost-effectiveness of reinfusing shed mediastinal blood has been questioned by several investigators. 209, 216, 217 The volume of blood collected is often small and the amount reinfused insufficient to decrease allogeneic RBC transfusion requirements. Potential complications resulting from transfusion of the blood include difficulties in diagnosing perioperative myocardial infarction, activation of the fibrinolytic and kallikrein-kinin system, enhanced reperfusion injury related to administration of activated platelets, and infection from contaminated blood. 217 Proponents of routine collection and reinfusion of shed blood cite studies demonstrating decreased allogeneic transfusion requirements 218, 219, 220 and emphasize that it is impossible to know in advance who will bleed excessively (and benefit from the technique) and who will not. 221 Processing of recovered blood obviates most of the problems potentially associated with reinfusion, but it is expensive, and the volume is often insufficient to make it worthwhile.

Orthopedic Surgery

Postoperative blood recovery is employed most often for total hip and knee arthroplasties. 222, 223, 224, 225, 226 Experience with the technique following spine surgery is limited. 227, 228, 229 Two questions arise: (1) is it effective and (2) is it safe?

The volume of wound drainage recovered in most series is 400 to 500 mL, but unilateral and bilateral hip and knee procedures are often reported together, making evaluation of the data difficult. The HCT of the reinfused blood is variable, depending on the procedure and the collection period. Most investigators do not provide these data. One group measured the volume and the HCT of recovered blood and found the mean postoperative RBC loss following total hip and knee replacement to be 55 ± 29 mL and 121 ± 50 mL, respectively. 230 The 6-hour wound drainage represented 8.7 and 16.8 percent of overall RBC loss during hospitalization for hip and knee replacements, respectively. Only three of 51 patients lost the equivalent of

one or more RBC units in recovered drainage. The volume of RBCs recovered after surgery bore no relationship to total perioperative RBC loss.

Although several groups have demonstrated decreased allogeneic transfusion requirements, 224, 225, 226 others have concluded that routine postoperative blood recovery is not justified, particularly in patients who participate in PABD programs. 230, 231, 232, 233 Selective use of postoperative blood recovery in patients undergoing bilateral total knee replacements or hip revision surgery or those in whom other forms of autologous transfusion are not employed may be costeffective.

There is considerable controversy regarding the necessity for processing the blood before reinfusion. Complement activation has been demonstrated in recovered blood, but not in the recipients of amounts up to 15 percent of estimated blood volume. 234 Recovered blood has elevated levels of cytokines (tumor necrosis factor-?, interleukin-1?, interleukin-6, interleukin-8) 235, 236, 237 and fibrin degradation products. 238, 239 Bone fragments, fat, and other debris are often visible, and fat particles too small to be removed by microaggregate filters have been demonstrated. 240 Levels of methylmethacrylate monomer in shed blood peak within minutes of drain insertion following total joint arthroplasty but are not detectable after the blood remains at room temperature for 6 hours—the maximum recommended collection period before reinfusion. 240

Despite the potential complications of reinfusing blood recovered after total joint arthroplasty, there are few reported complications. Faris et al 241 found a 22 percent incidence of febrile reactions associated with reinfusion of blood collected for 6 to 12 hours after operation, compared with a 2 percent incidence when the period of collection was 6 hours or less. Hypotension 242 and upper airway edema 243 have been reported with transfusion of unwashed blood. Despite laboratory evidence of activation of the coagulation and fibrinolytic systems, coagulation studies in recipients are no different than those in patients who receive liquid-preserved RBCs. 225 Reinfused RBCs have a normal life span. 244, 245, 246

COLLECTION OF PLATELET-RICH PLASMA

Cardiopulmonary bypass is associated with hemostatic abnormalities, the most significant being impaired platelet function. In an attempt to decrease postoperative bleeding and allogeneic transfusion requirements, autologous PRP may be collected before CPB and then reinfused following bypass. Conventional apheresis apparatus can be employed, but plasma collection kits designed specifically for intraoperative use with cell processing devices are preferable.

Conflicting results have been reported regarding the efficacy of PRP in reducing allogeneic transfusion requirements. Some differences can be attributed to study design, volume of collected platelets, time of collection (before or after heparinization), types of surgical procedures included, and absence of defined transfusion criteria. Two blinded, randomized studies did not demonstrate a decrease in transfusion requirements. Ereth et al 247 collected 600 to 700 mL of PRP in patients undergoing repeat valvular surgery and performed a sham procedure in control patients. Tobe et al 248 collected 8 to 10 mL/kg of PRP and reinfused it immediately in control patients and after heparin reversal in treated patients undergoing primary CABG. Shore-Lesserson et al 249 included patients undergoing repeat CABG and/or valve replacement in a prospective randomized controlled study in which treated patients had 1,000 mL of PRP (mean platelet count, 1.2¥1011 /L) removed. In addition to no effect on bleeding or transfusion requirements, there was a 60 percent incidence of hypotension requiring treatment when the PRP was reinfused. When the effect of fresh whole blood (mean volume 924 ± 130 mL) obtained by intraoperative hemodilution was compared with that of PRP (mean volume, 650 ± 124 mL; mean platelet count, 1.42 ± 0.74¥1011 /L), a comparable hemostatic effect that manifested as reduced postoperative bleeding was demonstrated, but neither technique influenced allogeneic transfusion requirements. 250 No differences in coagulation tests, platelet counts, chest tube drainage, or allogeneic transfusion requirements were demonstrated between control patients undergoing elective primary cardiac surgery and those who had PRP (mean volume, 892 ± 150 mL; mean platelet count, 1.4¥1011 /L) removed and reinfused. 251

In contrast to the foregoing, two other studies have demonstrated decreased blood loss and transfusion requirements. Christenson et al 252 studied a small group of patients undergoing repeat CABG in whom approximately 20 percent of circulating platelets were harvested. Blood loss and transfusion requirements were significantly decreased in treated patients. In addition, postoperative ventilation time and intensive care unit stay were shorter, and postextubation gas exchange was better. In a larger study, Armellin et al 253

evaluated 293 consecutive patients undergoing cardiac surgery, 147 of whom had PRP (10 mL/kg) removed before heparinization. Mediastinal drainage was less in treated patients during the first 12 postoperative hours, but no difference in total postoperative blood loss was noted. The volume of RBCs and fresh frozen plasma administered was less in treated patients than in control subjects. Transfusion criteria were defined in both of these studies.

What can be concluded from the aforementioned studies? As pointed out by Boldt 254 in his review, collection of PRP is time consuming, requires additional staff, and adds to the cost of surgery. However, collection and reinfusion of PRP are less expensive than transfusion of an equal amount of allogeneic fresh frozen plasma and platelets. Routine use of the technique in cardiac surgery does not appear warranted, but selective use may be beneficial. For example, patients undergoing complicated procedures who are expected to have prolonged CPB and significant blood loss may benefit.

An aliquot of the PRP can also be used for preparation of fibrin sealant or glue. 255 The PRP (or autologous cryoprecipitate prepared from predonated whole blood) is applied to bleeding tissues simultaneously with bovine thrombin and calcium. Numerous reports have documented improved hemostasis with application of fibrin sealant. 256 It is anticipated that a product prepared from solvent-detergent inactivated plasma recently licensed in the United States will reduce the collection of autologous blood for this purpose.