Transfusion of Blood Components

James M. Vogel, M.D.,* and Peter Vogel, M.D.†

The administration of whole blood to restore a depleted red cell mass or blood volume constituted, until recent years, the extent of blood usage. However, new techniques of centrifugation and preservation have provided blood products which may be used in the treatment of clotting defects or cytopenic states. The introduction of a closed system of sterile plastic tubing and bag that permits transfer of blood components with minimal risk of bacterial contamination has been largely responsible for the increased use of blood fractions. The efficient, economical use of blood implies that patients be transfused only with the specific component of blood required. Fresh whole blood may be separated by differential centrifugation into packed red blood cells, platelet concentrates, and plasma rich in labile clotting factors (fig. 1). Thus, as an example, a patient with chronic anemia, one with thrombocytopenia, and a patient with a clotting dyscrasia may all benefit from the same unit of blood. Blood replacement therapy will be presented in this article in terms of transfusion of cellular and non-cellular components.

Cellular Components

In most blood banks, red blood cells for transfusion are supplied as whole blood unless specifically requested as “packed” cells. The superiority of whole blood for acute hemorrhage is clear, but concentrated red blood cells may be used in any condition of anemia which does not require volume expansion. We estimate that 80–90 per cent of the transfusions in medical practice today may be given as packed cells, thereby retaining the plasma for other uses. Packed red cells prepared from blood collected in glass bottles must be used within 24 hours† because the stopper must be entered to remove the plasma, and there is risk of contamination. Red cells in plastic containers, however, may be stored for 21 days because plasma may be removed via a connecting satellite bag without violating the closed system. These cell suspensions with hematocrit values of about 70 per cent may be stored on an equal basis with whole blood. After 21 days of storage, they can be expected to demonstrate at least 70 per cent of red cell survival in vivo, 24 hours after transfusion.‡

There are many conditions for which packed cells are superior to whole blood. Packed cells minimize the chance of circulatory overload. In congestive heart failure, complicated by anemia, reduction of blood volume by venesection and replacement with concentrated cells may be lifesaving. Apparatus used for plasmapheresis,§ diagrammed in figure 2, may facilitate return of the patient’s own plasma-depleted red blood cells. This may be performed by disconnecting the bag of phlebotomized blood, centrifuging and then extracting the plasma before reinfusing the red cells. The needle may be kept patent by a continuous infusion of saline, or glucose in cases of congestive heart failure. Similarly, during exchange transfusion, the blood volume of some infants with elevated venous pressure may be lowered by removing whole blood while transfusing with packed cells.¶ Five hundred milliliters of plasma anticoagulated with acid-citrate-dextrose (ACD) contains approximately 10.5 g. of sodium;* hence administration of plasma-poor blood will reduce the amount of sodium infused and will be of further benefit to the patient in heart failure. In all chronic anemias where restoration of the oxygen carrying capacity is required, concentrated cells are preferable to whole blood because red-cell

* Clinical Associate, Medicine Branch, National Cancer Institute Bethesda, Maryland.
† Consultant Hematologist, The Mount Sinai Hospital, New York City.
mass may be raised without elevating the already expanded plasma volume.

Transfusion of packed red blood cells may avert or decrease transfusion reactions due to a plasma factor. In instances where group specific blood is not readily available, the use of red cells, i.e., group O to A or B recipients, with removal of four fifths of the plasma agglutinins, greatly minimizes the risk of hemolysis of the recipient's red cells, particularly when a patient with a small red-cell mass is transfused with plasma containing potent agglutinins. When transfusion reactions are thought to result from white cell or platelet antigens, red cells can be prepared by removal of the buffy coat from heparinized blood with the use of nylon filters. Alternatively, when blood is allowed to settle in an inverted position with an exit port at the bottom of the container, the red cells may be drawn off by gravity, allowing the majority of white cells and platelets to remain in the supernatant plasma.

Platelets

Bleeding secondary to thrombocytopenia can be stemmed in most instances by increasing the number of circulating platelets via transfusion. Administration of lyophilized platelets or platelet substitutes such as crude brain phospholipids or soy bean phosphatides in some circumstances has normalized in vitro clotting tests but has been only minimally effective in arresting hemorrhage. It appears that hemostasis in thrombocytopenic patients is a function of the intact viable platelet. Thrombocytes circulate in a predictable manner after infusion, provided that cellular or humoral antagonists are not present. The platelet count has been noted to be an accurate quantitative measure of probability of hemorrhage, but there does not appear to be a threshold level beyond which one can protect against bleeding. Grossly visible hemorrhage was noted by Gaydos et al. in only 1 per cent of hospital days in acute leukemic patients with platelet counts less than 20,000/cu. mm., as compared with bleeding on 31 per cent of the days in patients with counts less than 1000/cu. mm. Thus, transfusions have been given arbitrarily in most reported studies in an attempt to maintain the circulating level at 20,000/cu. mm. or greater.

Platelet levels have been elevated via transfusion prior to operation or before procedures such as cystoscopy or retrograde pyelography which could provoke bleeding in thrombocytopenic patients. Hemorrhage that may result following the rapid infusion of large amounts of stored compatible whole blood has been shown to be the result of thrombocytopenia since stored blood contains very few viable platelets. Such hemorrhage can be corrected by infusion of fresh thrombocytes. Platelet depression resulting from disease or iatrogenically produced as an adverse effect of many of the antitumor drugs has been corrected with exogenous platelets. The administration of platelets to thrombocytopenic patients, with acute leukemia in particular, has markedly lowered the incidence of serious or fatal hemorrhage. Hersh et al. noted that 66.8 per cent of these patients died from hemorrhage before the era of platelet transfusion as compared to 37.2 per cent after the institution of transfusion. Furthermore, the decrease in pulmonary, subarachnoid, and intracerebral bleeding was proportionately greater than in other types of bleeding. The decreased incidence of major bleeding episodes, especially in the central nervous system, emphasizes the importance of platelet infusions to terminate, as well as to prevent, bleeding.
The short lifespan of platelets necessitates frequent transfusion. When supplied in fresh whole blood, the red cells that are given with the thrombocytes may overload the circulation. To avoid this, platelets may be supplied in platelet rich plasma (PRP), or if the increased volume of plasma cannot be tolerated—in platelet concentrates (PC). Fresh blood drawn into the primary ACD-containing bag of a double plastic pack (fig. 2) may be centrifuged at the rate of 1,500 × g for 3 minutes and the supernatant plasma containing 90 per cent of the platelets expressed into the satellite bag. The latter can be disconnected from the packed red cells remaining in the primary bag. Centrifugation of the plasma in the satellite bag at 1,500 × g for 15 minutes will drive the platelets into a button leaving a platelet-poor supernate. Platelet concentrates may be prepared by decanting all but 25 to 50 ml. of plasma and resuspending the platelets by vigorously rubbing the bag. If the donor is bled into the primary of a triple bag pack, platelet concentrates can be prepared from PRP in the first satellite bag. The platelet-poor plasma may then be decanted into a second satellite bag and is suitable for freezing to provide a source of labile clotting factors. Preparation of concentrates may produce platelet clumps which exhibit poor platelet recovery and survival. Acidification of the PRP prior to concentrating the platelets, by adding 7.5 ml. of NIH Formula A ACD to each 100 ml. of plasma or addition of 1 ml. of 0.25 M citric acid for every 100 ml of plasma, will lower the pH to 6.4–6.8 and diminish platelet clumping.13

Platelets may be obtained from fresh units of whole blood or prepared by means of plasmapheresis14 (fig. 2). Donors undergoing plasmapheresis may donate up to 1.5 liters of plasma per week at one or more sessions with little depletion of formed elements and only slight diminution of serum protein.15 Since only one unit of fresh blood may be donated every six weeks, it is apparent that 36 times the quantity of PRP may be donated over this period by a donor undergoing regular plasmapheresis. This procedure is particularly applicable in extracting platelets from donors with higher than normal platelet counts, who may be used repeatedly. If more extensive platelet removal is required, platelets may be concentrated and platelet-poor plasma returned with the red cells to prevent protein depletion.

The overall supply of platelets is dependent upon the availability of fresh blood, so that a number of investigators have developed methods for preservation and storage. Slow freezing of platelet concentrates in a glycerol medium has been reported by Cohen and his co-workers,16 while Tullis et al.17 have reported remarkable stability and satisfactory elevation of circulating platelets after transfusion of material stored in gelatin at 4°C, following careful separation from plasma. Djerassi18 adds 2.5 g. of DMSO in 5 per cent dextrose to 10 units of concentrated platelets prior to freezing.
After thawing, 50 ml. of platelet-poor plasma is used as a suspending medium. Transfusions are reported to be nearly 50 per cent as effective as an equivalent amount of freshly prepared platelet concentrate, but adverse effects of nausea, vomiting and pain at the site of injection have been noted.

The response to transfused platelets varies with the individual and with the clinical state. In instances of sepsis, hemorrhage, or fever infused platelets are not as effective in elevating the circulating levels. On the average the number of platelets in one unit of whole blood or one unit of PRP (250–300 ml.) is $1 \times 10^{11}$ cells; this amount will raise the circulating platelet count 12,500/cu. mm. in a recipient having a one square meter body surface area, one hour after transfusion. This figure represents recovery after 1 hour of only 30–40 per cent. Acidified concentrates are about 90 per cent as effective as PRP.

Transfused platelets appear to elevate the count independently of the pretransfusion level. PRP infused immediately after donation offers the same rate of survival as cells stored up to seven hours prior to transfusion. PRP stored for 24 hours and 48 hours will be only 62 per cent and 37 per cent as effective, respectively, as freshly infused material in elevating the platelet count. This approximates the in vivo survival of platelets, so that survival appears to be same whether the platelets are refrigerated and stored in the collection bag or present in the circulation.

In order to decrease the frequency of administration, we transfuse patients with platelets derived from at least 4–6 units (250–300 ml/unit) pooled from donors of the same ABO blood group. If the platelets do not aggregate, there is little difference in response after passage through a small platelet filter, prior to infusion. Type-specific PRP is transfused but nonspecific concentrates have been given with little difficulty since the plasma volume is small. It may be important to transfuse type-specific concentrates as well as PRP, because Aster has shown that platelet recovery is lower by ABO incompatibility between donor platelet and recipient serum. The survival of remaining platelets in these instances was not altered.

The development of antibodies to platelets following transfusion has been noted infrequently, probably because many of the recipients have been patients with acute leukemia treated with immunosuppressive drugs. Patients with aplastic anemia not given these drugs have not uncommonly developed antiplatelet antibodies with a concomitant decreased response to platelet infusion. Complement-fixing antibodies against platelets have been detected frequently in the serum of recipients when a decreased response or a shortened survival was demonstrated; however, the presence of complement-fixing antibodies was not necessarily associated with a decreased response to transfusion. Repeated platelet transfusions can be associated with an incidence of fever-chill reactions as high as 20 per cent; Aster et al. reported the presence of platelet antibodies in 11 of 32 such patients. The frequency of development of antibodies in patients with fever and chills was significantly higher than in patients with no reaction following platelet infusion. Certain diseases such as idiopathic thrombocytopenia purpura are associated with an antiplatelet factor, although a specific antibody has not been identified. This probably accounts for the low recovery and survival following platelet infusion in these disorders. Massive platelet transfusion may elevate the count prior to surgical procedures such as splenectomy in these patients, but chronic transfusion has no merit.

White Blood Cells

Deficiency of white blood cells in the peripheral blood can be considered in terms of decreased levels of total circulating granulocytes. Granulocytopenia is produced by most of the antitumor drugs; it is in this situation of presumed short term white blood cell depression that granulocyte transfusions have had widest use. Transfusion of these cells provides protection against infection which threatens survival of the patient and limits the potential effectiveness of therapy of the underlying disease. Yields of transfused granulocytes, obtained from normal and chronic myelocytic leukemic donors, based on a one hour post-infusion white blood cell increment, approximated 5 per cent. However, the recipients in these instances were leukopenic and the pos-
sibility of sequestration in tissue pools must be considered. According to Freireich et al., the lower the pretransfusion granulocyte count, the lower the percentage recovery of transfused granulocytes. When transfused with labeled leukocytes, patients with chronic myelocytic leukemia having white blood counts ranging from 23,000 to 50,000 cells/cu. mm. and presumed nondepleted tissue pools, showed recovery of labeled cells ranging from 29 to 54 per cent at five minutes. Thus, it appears that if there is no leukopenia, recovery of transfused leukocytes is greater.

Based on the size of the total blood granulocytic pool (TBGP) and evaluating the low recovery rate of 5 per cent, it is estimated that approximately \(1 \times 10^{11}\) cells are needed to replace 25 per cent of the TBGP in a recipient per square meter of body surface. This is the number of white cells contained in 30-40 units of normal whole fresh blood. Extraction of granulocytes from normal blood appears to be impractical because of the small yield per unit, thus the many donors required. Continuous flow separation of granulocytes from a single donor by means of differential centrifugation has been attempted by several investigators, but does not appear to provide enough granulocytes to obtain a satisfactory clinical response. However, patients with chronic myelogenous leukemia with a high proportion of polymorphonuclear or band forms and with peripheral white counts in excess of 100,000 cells/cu. mm. have been used successfully as granulocytic donors. Transfusion of \(1 \times 10^{11}\) granulocytes per square meter of body surface area have produced, one hour after infusion, an average increment of 1,000 mature myeloid cells.

A single leukopheresis of a chronic myelocytic leukemia donor can provide, on the average, the equivalent number of granulocytes contained in 40 units of normal blood. Utilizing the plasmapheresis apparatus diagrammed in figure 2, 500 ml. of blood are collected in a primary plastic bag containing ACD. The unit of blood is disconnected from the system and the needle kept patent with a slow saline infusion. The blood is then spun at 40 \(\times\) g for 30 minutes and the centrifuge head allowed to come to a complete stop without braking. The plasma rich in white blood cells is then decanted through the sterile connecting tubing into a satellite bag and is ready for transfusion. The tubing is doubly sealed and the packed red blood cells in the primary bag are then reinfused into the donor. The procedure may be repeated using additional sets of primary and satellite bags. If the volume is critical for the leukopenic recipient, the white blood cells may be concentrated by centrifuging the plasma in the satellite bag at 1,100 \(\times\) g for 10 minutes and the cell free supernate removed prior to infusion. Morse et al. have reported that removal of up to 20 liters of blood in one week from a chronic myelocytic leukemic donor by this method has produced only transient thrombocytopenia and slight temporary changes in the white blood count.

Plasma rich in white cells may be administered directly or through a platelet-type filter to decrease cell loss. Since plasma rich in white cells is contaminated by red cells on an average of one red blood cell for every three white blood cells, donor and recipient are crossmatched prior to transfusion. Reactions related to granulocytic transfusions have occurred in 50 to 60 per cent of the leukopenic recipients. The majority of these were of the fever-chill type. Less than 10 per cent of chronic myelocytic leukemia transfusions were accompanied by dyspnea, tachypnea, cyanosis, and rarely pleural effusion. Adverse respiratory effects were especially marked when the patient had pulmonary involvement prior to transfusion. Sequestration of transfused white blood cells in lung tissue is a known phenomenon and it is believed that respiratory symptoms are directly related to pooling in this area. Leukocyte-antibody reactions have been documented and shown to bear causative relation to fever-chill responses.

The efficacy of granulocytic transfusion is a subject of debate. Nevertheless, there are dramatic instances of marked change in the clinical course directly following white blood cell transfusion. Freireich et al. reported that 38 per cent of 80 febrile patients, most of whom had not responded to antibiotics, became afebrile in 12 hours following white blood cell infusion. An additional 13 per cent became afebrile over the next 24-36 hours. Most of the patients were given antibiotics at the same
time and it is not possible to say whether drugs, cells or both were responsible for lysis of fever. However, as the dose of granulocytes was increased the percentage of patients responding with return of temperature to normal levels increased, suggesting an effect of the cells. Of 21 leukopenic patients with documented Gram-negative sepsis, 14 had decreased fever and 9 could be considered clinically cured following chronic myelocytic leukemic transfusions in conjunction with antibiotics.

Myeloid grafts have been reported following chronic myelocytic leukemic transfusion. Persistence of chronic myelocytic leukemic cells as noted by cytogenetic identification of an abnormality of the 21 (Philadelphia, Ph+) chromosome was detected for 19, 39, and 52 days, respectively, following administration of white blood cells in 3 cases cited by Levin et al. All 3 individuals were leukemic children who had received individual doses of 1.9 to 8.8 x 10^11 nucleated cells in 1 to 6 separate leukocytic transfusions. Mild hypogammaglobulinemia was noted in all 3 children, supporting the idea of impaired competence of the immune mechanism. In one subject the level of circulating granulocytes reached 31,000/cu. mm. 35 days post-transfusion, at a time when 90 per cent of the scored metaphases contained the Ph+ chromosome.

**Noncellular Components**

The noncellular components of blood are used principally in three situations: (1) to correct acute depletion of blood volume, (2) to supply deficient clotting factors and, (3) to augment intravascular albumin levels in cases of decreased production or increased loss of circulating protein. Substances available in blood banks today are plasma in fresh frozen, cryoprecipitated, liquid, or lyophilized form; serum albumin; fibrinogen; and plasma protein fraction (PPF) (plasma with fibrinogen and globulin removed).

**Plasma**

The role of plasma in transfusion has changed in the last 20 years largely because of the availability and superiority of whole blood for the treatment of hemorrhage. The usual availability of several units of universal donor Group O blood in most banks has decreased the emergency need for plasma. Only in special situations of hypovolemia with hemococoncentration, as in adrenal insufficiency or following acute loss of plasma as in burns or fulminant pemphigus, is plasma preferred to whole blood. In military injury the use of plasma has decreased but it is still useful because it may be stored, transported without refrigeration, and in the case of dried plasma, rapidly reconstituted. If a unit is prepared from large plasma pools, plasma may be safely administered without regard to blood type.

The administration of pooled plasma obviates the necessity for red-blood-cell typing, but the high incidence of serum hepatitis has discouraged its use. Several series show that the incidence of serum hepatitis following plasma infusion varies directly with the number of donors constituting the pool. Thus, the incidence of hepatitis was 7.3 per cent resulting from pools up to 200 donors while 4.5 per cent in pools from 25–30 donors and only 2.08 per cent when derived from 8–12 donors. In order to lessen the possibility of transmission of hepatitis, plasma is processed in many centers from single units of blood. Recent evidence indicates that storage for 6 months or longer at 31°C., but not at room temperature (22.0°C.), will markedly lower viral hepatitis infectivity.

The advantage of plasma over whole blood lies in treatment of coagulation deficiencies because in these conditions clotting factors can be supplied quickly and in great quantity without raising the hematocrit value above the normal. Labile clotting factors present in a red-cell-free medium may be conveniently preserved. All factors are found in frozen liquid or frozen dried plasma in high titer, and activity of all factors, except for V and VIII, is present in plasma refrigerated at 4°C. for 20 days, then stored at −20°C. Factor XI (PTA) activity may actually be increased in aged plasma stored at −15°C. when compared with fresh plasma. The relation of storage to labile factor activity has not been fully established. New methods of collection may change the present blood banking concept in regard to the rapid disappearance of the labile clotting substances. Rosenthal and Sloan found about 50 per cent of Factor VIII
(AHG) activity in plasma obtained from blood after 21 days when compared with a previously established figure of 30-37 per cent in plasma of similar age undergoing similar treatment. However, they tested blood collected and stored in plastic bags, and it is conceivable that prior experience was the result of testing blood from glass containers.

At present frozen plasma is prepared from freshly donated blood after removal of all cellular elements, including platelets. If blood is collected in a double plastic pack, plasma may be expressed into a satellite bag with retention of cellular elements in the primary bag. Plasma in the satellite bag may be frozen as individual units or pooled and subjected to freeze-drying. Brinkhouse et al. showed that frozen plasma when reconstituted contains an amount of the labile antihemophilic globulin (AHG) comparable to that retained in frozen liquid plasma. Frozen fresh plasma may be stored at room temperature indefinitely, but the frozen liquid variety kept at the optimum temperature −20 to −30°C can be used to supply labile clotting factors, for no more than a year following donation.

One should appreciate that clotting defects do not present in an all or none manner, but that variable suboptimal levels may be operative. Therefore, the volume and frequency of plasma administration to correct deficiencies varies according to the clinical response. We prefer to give fresh frozen liquid plasma prepared in type-specific units because fresh frozen plasma is made from pooled plasma where the risk of hepatitis is high. Unexpected bleeding during or following major operations occurs most often because of inadequate hemostasis or when many units of aged banked blood, lacking viable platelets, induce thrombocytopenia. Rarely, labile clotting factors may be low or decreased during massive blood replacement particularly in cases where a borderline level was in effect prior to operation. Since the result of clotting studies may not be available immediately, fresh whole blood or fresh frozen plasma may be given when indicated by the clinical situation.

**Antihemophilic Concentrates**

Recently a concentrated material for use in hemophilic patients has been prepared by Pool et al. The product is 20–30 times as potent as plasma and readily prepared. After collection, blood is centrifuged and the plasma expressed into a satellite bag. The bag is immersed in a freezing mixture of alcohol and dry ice. The quick-frozen plasma is placed in a refrigerator at 4°C and allowed to thaw for 24 hours. Upon thawing, a precipitate forms which contains 70 per cent of the original antihemophilic globulin. Centrifugation settles the precipitate in the bottom of the bag. After decantation of supernatant, the precipitate rich in antihemophilic globulin is frozen. When needed, the material is dissolved in citrated saline at room temperature, pooled and infused. When given at 12-hour intervals, the material can provide and maintain levels of antihemophilic globulin adequate to control most bleeding problems. Concentrated antihemophilic factor (AHF) prepared with modifications by Johnson has been shown to possess 60–70 times the potency of an equal volume of plasma and has been used successfully to control bleeding in hemophiliacs undergoing major surgery.

**Albumin**

Normal serum albumin contains 50–60 per cent of the circulating protein, and by virtue of low molecular weight (69,000) exerts 80 per cent of the plasma colloid osmotic pressure. Twenty-five grams of albumin is the osmotic equivalent of 500 ml of citrated plasma. Thermal treatment of Cohn fraction V produces a hepatitis-free product. Albumin is available in a 5 per cent buffered saline or a 25 per cent “salt-poor” form. The sodium content of the salt-poor as compared with standard albumin and plasma can be seen in table 1.

The use of albumin as a plasma expander was promoted by the military during World War II because it could be transported and administered in a concentrated form with retention of a low viscosity. Albumin has been shown to be effective in several types of shock, but its ultimate plasma expanding activity depends upon the availability of extravascular fluid. Thus, in shock with large blood volume

TABLE 1. Instruction Sheet, Standard Navy Normal Serum Albumin

<table>
<thead>
<tr>
<th>Equivalent Volumes</th>
<th>Sodium Content (g/100 ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>450 ml.</td>
<td>Circulating plasma</td>
</tr>
<tr>
<td>500 ml.</td>
<td>ACD plasma</td>
</tr>
<tr>
<td>100 ml.</td>
<td>5% standard albumin</td>
</tr>
<tr>
<td>100 ml.</td>
<td>25% “salt-poor” albumin</td>
</tr>
</tbody>
</table>

deficit, as a result of dehydration, albumin is distinctly less effective. However, when given in conjunction with solutions of crystalloids, it is a good substitute for plasma since it is free of the hepatitis virus. Albumin has been infused to correct hypoproteinemic states because these conditions are generally characterized by deficiency of albumin resulting from a decreased or impaired protein intake, excessive protein loss into the gastrointestinal lumen or via renal tubules, or resulting from decreased hepatic synthesis. Repeated removal of large amounts of transudates from the peritoneal or pleural spaces, draining exudative wounds and transudation from large weeping surfaces as in pemphigus or burns are other examples of albumin loss. Replacement is usually ineffective or at best only temporarily effective in raising the plasma albumin level because of the rapid turnover of this substance. Albumin tagged with radioactive iodine has an average intravascular half life of 17 days in normal subjects. This may be markedly reduced in patients with major albumin loss, so that repeated infusions are necessary to obtain a satisfactory response. Repeated albumin administration to patients with the nephrotic syndrome produced only a transient rise in serum albumin and a temporary edema-free state in some of the patients. Albumin transfusions given to patients with protein-losing enteropathies have been virtually without effect. Transfusions given to patients with low albumin levels resulting from impaired hepatic synthesis have been slightly more beneficial. Selected cirrhotic patients have been diuresed and kept edema-free on a regimen of 50 g of albumin per week after a 700 to 1,000 g loading dose. Patients with congenital hypalbuminemia have been shown to have a prolonged intravascular albumin half-life of approximately 50 days. The low turnover rate in these patients who normally display no peripheral edema permits correction of mild symptoms of lassitude and fatigue with as little as 25 g of albumin per week. It has been argued that infusion of albumin to surgical patients depleted of this substance will enhance retarded wound healing. However, patients with congenital hypalbuminemia, who have undergone surgery, have demonstrated normal postoperative wound healing.†

Fibrinogen

Desiccated human fibrinogen prepared by the Cohn cold-ethanol fractionation procedure is available commercially in 1 and 2 g vials that may be reconstituted with sterile water to form a one per cent solution. In spite of ultraviolet exposure during preparation, fibrinogen is not free of hepatitis virus as is serum albumin. From 1957-1961 Cronberg et al. observed 15 cases of hepatitis in Sweden following administration of fibrinogen. Six of these patients did not receive a blood transfusion. Gamma globulin given to 4 of the 15 subjects at the same time as fibrinogen did not protect against liver disease. The high incidence in this report of serum hepatitis following fibrinogen infusions was attributed to a specific batch of infectious material. Fibrinogen used for these patients was prepared by glycine extraction from plasma pooled from 600 to 1,000 donors, so that one unit may have contaminated the large supply. Reduction of pool size diminishes the incidence of hepatitis. The danger, however, is still great enough so that the use of fibrinogen should be limited to those instances where the quantity of fibrinogen in whole blood or plasma would increase the blood volume dangerously or where rapidity of administration is necessary. Fibrinogen should be administered only when hemorrhage occurs because a low level of this protein may be adequate in the absence of bleeding. Clinical conditions associated with a state of hypofibrinogenemia resulting from defibrination may be exacerbated by administration of fibrinogen, and may respond to an infusion of heparin. Similarly, a fibrinolytic

† Waldmann, T. A.: National Cancer Institute Bethesda, Md., personal communication.
condition can be prolonged by fibrinogen, and may require epsilon aminocaproic acid if the fibrinolysis is not secondary to intravascular clotting.20

One gram of commercially prepared fibrinogen is stated to contain the equivalent of 75–100 ml of AHG plasma. The use of this material for correction of bleeding in hemophilia A (Factor VIII deficiency) was initially discredited because of the inconstancy of the AHG content coupled with the increased danger of hepatitis from pooled material. Improved quick-spin freezing and lyophilization without excessive heat have produced fibrinogen with a reproducible AHG content.44 The use of plasma from only two donors to produce a unit of fibrinogen rich in AHG has minimized the danger of hepatitis. The use of these preparations has been considered by some45 to be superior to fresh frozen plasma in the treatment of Factor VIII deficiency. However, the limited availability of this product has hampered broad clinical testing.

Summary

Single units of whole blood may be conveniently, economically, and efficiently processed to supply individual preparations of red blood cells, platelets and plasma. Although whole blood may be required for acute hemorrhage, concentrated red blood cells may be administered for other anemias. This fractionation salvages 250–300 ml of platelet containing plasma per unit of whole blood for the preparation of platelet or plasma transfusions. In certain circumstances, transfused "packed" cells may, in fact, be more desirable than that of whole blood for optimal management of the primary disease. Platelets may be infused to thrombocytopenic patients in platelet-rich plasma or in platelet concentrates. In the absence of bleeding or sepsis administration of 1 × 10^{11} platelets will raise the circulating platelet count by an increment of 12,500 cells/cu. mm. in a recipient of one square meter one hour after transfusion. Platelet-poor plasma can be frozen, lyophilized or cryoprecipitated and in these forms it can supply labile clotting factors. Granulocytes, obtained from chronic myelogenous leukemic donors, have been transfused into leukopenic subjects and have been associated with beneficial changes in their clinical courses. Several instances of homologous myeloid grafts have been reported following the administration of these cells.

Albumin infusions are not associated with hepatitis, and they may be used for volume expansion although the beneficial effects depend upon the availability of extravascular fluid. Hypoalbuminemia associated with a rapid turnover of intravascular protein responds poorly even to massive albumin transfusions. The decision to employ fibrinogen preparations should take into consideration the frequency of hepatitis associated with these transfusions. Hypofibrinogenemia secondary to defibrination or fibrinolysis may be exacerbated by the administration of fibrinogen and may respond to heparin or epsilon-aminocaproic acid.

References

6. Instruction Sheet enclosed in Navy Package (Normal Serum Albumin).
10. Klein, E., Farber, S., Djerassi, I., Toch, R., Freeman, G., and Arnold, P.: The preparation and clinical administration of lyophilized platelet material to children with acute leuk-


