Kirk-Othmer Encyclopedia of Chemical Technology.

FRACTIONATION, BLOOD, CELL SEPARATION

Whole blood is seldom used in modern blood transfusion. Blood is separated into its components. Transfusion therapy optimizes the use of the blood components, using each for a specific need. Red cell concentrates are used for patients needing oxygen transport, platelets are used for hemostasis, and plasma is used as a volume expander or a source of proteins needed for clotting of the blood.

The discovery in 1900 of the existence of blood groups, together with improved understanding of the importance of sterile conditions, paved the way to modern blood transfusion therapy. In 1915, the feasibility of storage of whole blood was demonstrated. During World War I, the optimal concentration of citrate for use as an anticoagulant was determined. This anticoagulant was used until 1942, when the acid–citrate–dextrose (ACD) solution was developed.

A method for the fractionation of plasma, allowing albumin, γ-globulin, and fibrinogen to become available for clinical use, was developed during World War II (see also Fractionation, blood–plasma fractionation). A stainless steel blood cell separation bowl, developed in the early 1950s, was the earliest blood cell separator. A disposable polycarbonate version of the separation device, now known as the Haemonetics Latham bowl for its inventor, was first used to collect platelets from a blood donor in 1971. Another cell separation rotor was developed to facilitate white cell collections. This donut-shaped rotor has evolved to the advanced separation chamber of the COBE Spectra apheresis machine.

1. Blood Component Therapy

Blood is composed of a cellular portion, the formed elements, suspended in plasma. The formed elements constitute approximately 40–45% of the blood volume, ie, the hematocrit. When a test tube with blood is centrifuged, the formed elements are packed onto the bottom of the tube, leaving plasma on top (Fig. 1).

The formed elements consist primarily of red blood cells, ie, erythrocytes. Less than 1/600 of the total volume of the formed elements is composed of white blood cells, ie, leukocytes, and less than 1/800 are platelets, ie, thrombocytes. Table 1 gives the typical constitution of human blood.

Each component of blood has a function in the body. Red cells transport oxygen and carbon dioxide between the lungs and cells in the tissues. White cells function as defense of the body. Platelets are important for hemostasis, ie, the maintenance of vascular integrity. Plasma, an aqueous solution containing various proteins and fatty acids, transports cells, food, and hormones throughout the body. Some proteins in plasma play a role in clotting, others are messengers between cells.

A new field of transfusion medicine, cell therapy, has developed with the better understanding of the function of different cell types in the body. In cell therapy, various malignancies are treated by transfusion of specific cell types from blood. Therefore, more and more specialized methods for separating blood into the various components are required.

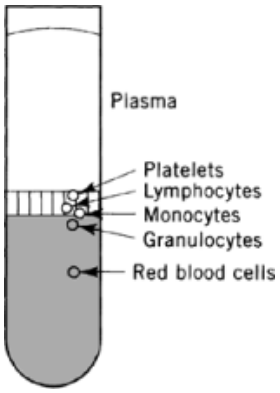

Fig. 1. Distribution of component cells by density in a centrifuged sample of human blood.

Table 1. Hematological Values of Human Blood Components

Parameter	Value range
Physical properties	
blood volume by body weight, mL/kg	80–85
blood osmolarity, mOsm	285–295
blood pH	7.35–7.45
hematocrit, vol %	35–48
Plasma protein fraction	
fraction of plasma, wt %	7–9
concentration, g/100 mL plasma	6.0–8.4
albumin, mass % of protein	50–80
globulins, mass % of protein	15–45
fibrinogen, mass % of protein	3–8
Cell components	
erythrocytes[a]	
10^9 cells/mL	4.8–5.4
fraction of cells, vol %	91
leukocytes[b]	
10^6 cells/mL	4–11
fraction of cells, vol %	5
granulocytes, vol % WBC	55–65
monocytes, vol % WBC	3–9
lymphocytes, vol % WBC	25–33
thrombocytes[c]	
10^6 cells/mL	200–400
fraction of cells, vol %	4

[a] Red blood cells (RBC).
[b] White blood cells (WBC).
[c] Platelets.

1.1. Collection of Blood and Blood Components

A number of developments since the 1960s have fueled the need for advanced blood cell separation technology. Advancements in medicine have resulted in increasing requirements for blood and its various cellular and plasma-derived components. National programs strive for self-sufficiency in meeting the demand for blood-derived products. Increased awareness of transfusion transmitted disease has resulted in a quest for a 100%

safe blood supply even though chances of transmitting blood-borne disease are very slim. In the United States chances of contracting hepatitis A or B through blood transfusion are less than 1 in 20,000, and transmission of the HIV virus through blood transfusion is estimated to be less than 1 in 300,000 in 1993.

Blood can be collected in the form of whole blood donations. In the United States, one unit, ie, 450 mL, of blood is collected from a healthy volunteer blood donor who is allowed to donate blood once every 10 weeks. A unit of blood is typically separated into a red cell fraction, ie, red cell concentrate; a platelet fraction, ie, random donor platelets (RDP); and plasma.

Blood components are also collected through apheresis. In apheresis, advanced blood cell separators are used to collect one or more specific blood components from a donor. The cell separators collect blood into a separation chamber, isolate the desired blood components, and return the blood components not needed to the donor. This procedure is performed on-line within one sterile disposable tubing set. The two principal components collected through apheresis are plasma and single-donor platelets (SDP).

The objectives of collection, separation, preparation, and storage of blood components are (*1*) to provide a safe blood product through careful screening and testing of the donor and collected product; (*2*) to maintain sterility of the product by adequate cleansing of the venepuncture site(s) and sterile processing methods which are essential to avoid bacterial contamination of the products; (*3*) to maintain viability and function of the components, ie, separation and storage methods need to be optimal for the specific transfused product; and (*4*) to make optimal use of blood components by transfusion of only those components indicated for the malignancy of the patients.

2. Function and Use of Blood Components

Primary blood components include plasma, red blood cells (erythrocytes), white blood cells (leukocytes), platelets (thrombocytes), and stem cells. Plasma consists of water; dissolved proteins, ie, fibrinogen, albumins, and globulins; coagulation factors; and nutrients. The principal plasma-derived blood products are single-donor plasma (SDP), produced by sedimentation from whole blood donations; fresh frozen plasma (FFP), collected both by apheresis and from whole blood collections; cryoprecipitate, produced by cryoprecipitation of FFP; albumin, collected through apheresis; and coagulation factors, produced by fractionation from FFP and by apheresis (see Fractionation, blood–plasma fractionation).

2.1. Red Blood Cells

Red blood cells (RBC) transport and deliver oxygen and carbon dioxide between the tissues and lungs. Red blood cell transfusions increase the oxygen carrying capacity in anemic patients.

Packed red cells are prepared from whole blood. These are collected in blood collection units having integrally attached transfer packs. The red cells are sedimented by centrifugation, and the plasma and buffy coat are expressed from the bag. Further processing of the packed red cells may be needed for a number of clinical indications. To reduce the white blood cell (WBC) contamination in a red cell product, two separation techniques are used.

The red cells may be washed with physiologic saline by using a number of centrifugation and dilution steps. Granulocytes, which form aggregates with platelets in the red cell product, are removed. The total leukocyte reduction varies from 70 to 95%. Approximately 15% of the red cells are lost in this process, and 95% of the plasma from the packed red cells is removed; this may be advantageous in patients having an immunoglobulin deficiency.

The red cells also may be filtered to reduce the white cell content. This technique is needed if there is a chance of the patient developing graft versus host disease (GvHD), ie, transfused white cells attack the cells of the patient.

Red cells may be salvaged for autologous transfusion from blood shed during a procedure in the operating room. This process is called intraoperative blood cell salvage. Shed blood is collected from the operative wound and then filtered, separated, washed, and centrifuged. The red cells, the only component of the shed blood not affected by the operation, are separated by centrifugation in a special chamber. While centrifuging these cells, physiologic saline is circulated through the bed of red cells to wash any debris out of the red cell layer, eg, free hemoglobin, cell stroma, and bone chips.

2.2. White Blood Cells

White blood cells, or leukocytes, have varying function and morphology. Mononuclear leukocytes include lymphocyte B and T-cells, monocytes, and progenitor cells. Polynuclear granulocytes include neutrophils, basophils, and eosinophils. The most important groups in cell separation are lymphocytes, monocytes, and granulocytes.

Contamination of blood products with lymphocytes can lead to transfusion-induced reactions ranging from a mild fever to severe reactions such as alloimmunization and graft versus host disease (GvHD), in which the transfused lymphocytes (graft) survive the defensive immune reaction of the patient (host) and start a reaction which destroys the cells of the host. The patient also may develop an immune response to the human leukocyte antigen (HLA) type of the graft's cells and reject all platelet transfusions that do not match their own HLA system. The HLA system, found on blood platelets and lymphocytes, is more complicated than, but similar to, the ABO blood group system of red cells.

Although the significant efforts in blood cell separation (ca 1993) are aimed at producing virtually leukocyte-free blood products and improving both cell separation and filtration, leukocyte collection is required for some use in blood transfusion therapy. Lymphocytes produce cytokines, which play a role in the communication between blood cells and can be used for the production of interferons for diabetes and interleukins for medical research (see Insulin and other antidiabetic drugs). Natural killer cells (NK-cells), a lymphocyte subgroup, may be applied in the treatment of immune disease. Typically the strategy is to collect the patient's own lymphocytes by apheresis, separate out NK-cells, culture and treat them *ex vivo,* and reinfuse them. Transfusion of leukocytes also may be beneficial in fighting sepsis in neonates and granulocytes may be transfused to cleanse the blood from bacteria. White cells also are transfused in the collection of blood-forming cells, or stem cells; this is discussed separately.

2.3. Platelets

Blood platelets play a key role in the prevention of blood loss from intact vessels, and the arrest of bleeding from injured vessels. They release adenosine diphosphate [58-64-0] (ADP) and thromboxane A_2 [57576-52-0] which results in vascular contraction and, indirectly, in the formation of fibrin clot. Platelet transfusions are indicated for patients with thrombocytopenia, ie, a shortage of healthy platelets; or thrombocytopathy, ie, platelet malignancy associated with spontaneous hemorrhages.

Transfusion-induced autoimmune disease has been a significant complication in the treatment of patients who require multiple platelet transfusions. Platelets and lymphocytes carry their own blood group system, ie, the human leukocyte antigen (HLA) system, and it can be difficult to find an HLA matched donor. A mismatched platelet transfusion does not induce immediate adverse reactions, but may cause the patient to become refractory to the HLA type of the transfused platelets. The next time platelets with an HLA type similar to that of the transfused platelets are transfused, they are rejected by the patient and thus have no clinical efficacy. Exposure to platelets originating from different donors is minimized by the use of apheresis platelets. One transfusable dose (unit) of apheresis platelets contains $3 - 5 \times 10^{11}$ platelets. An equal dose of platelets from whole blood donation requires platelets from six to eight units of whole blood. Furthermore, platelets can be donated every 10 days, versus 10 weeks for whole blood donations.

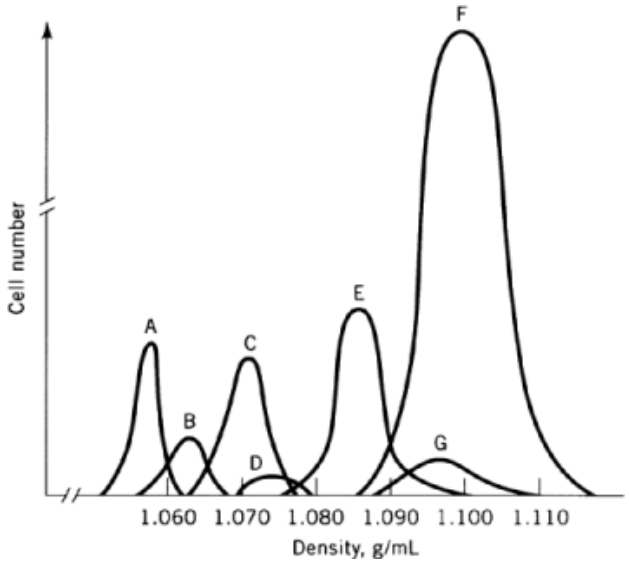

Fig. 2. Mass density distribution of blood components: A, platelets; B, monocytes; C, lymphocytes; D, basophils; E, neutrophils; F, erythrocytes; and G, eosinophils.

White cell contamination of a platelet product can induce GvHD. It is believed that GvHD can be minimized by a contamination of less than 5×10^6 white cells per therapeutic dose of platelets, ie, $3 - 5 \times 10^{11}$. Blood cell separation technology is directed toward consistently achieving this goal. Combinations of centrifugation, countercurrent washing, filtration, and uv-irradiation are being investigated to avoid alloimmunization or GvHD.

2.4. Stem Cells

Stem cells, or hematopoietic progenitor cells, have the capability of endlessly reproducing themselves and forming new blood cells. High dose chemoradiotherapy, used in the treatment of a number of malignant diseases, destroys all cells in the body that have reproducing capabilities, including stem cells. Patients are treated after each round of chemoradiation therapy by transfusion of stem cells to reconstitute their own blood supply. Stem cells may be collected either from the bone marrow or from the peripheral blood stream, ie, administering growth factors to patients cause the release of stem cells into the blood stream. Stem cells have separation properties similar to lymphocytes and monocytes, and therefore are found in the lower layers of the buffy coat.

3. Centrifugation Methods

Each type of blood cell has its own distribution of mass densities (Fig. 2). Most blood cell separators are based on the formation of blood components into layers by density gradient only. Some cell separators, ie, Haemonetics MCS, apply methods based on a combination of mass density and cell size.

Table 2. Properties of Blood Components

Component	Averagedensity, g/mL	Diameter, μm	Shape
plasma	1.025–1.029		
platelets	1.040	3	disk, 1-μm thick
white blood cells			
lymphocytes	1.070	8–15	spherical
monocytes	1.075–1.080	15–22	spherical
granulocytes	1.087–1.092	10–14	spherical
red blood cells	1.093–1.096	7.2–7.9	donut, 2-μm thick

3.1. Density Gradient Separation

Based on specific density, each cell in a test tube finds its own position (see Fig. 1), ie, red cells at the bottom, then granulocytes, monocytes, lymphocytes, platelets, and plasma on top. Table 2 lists average mass density of the cellular components of blood. The actual numbers vary slightly from person to person.

Many cell separation methods are based on the formation of layers by mass-density gradient. The simplest method is based on spinning down a bag of blood and expressing off the different layers. The more complex apheresis machines, eg, Baxter Fenwall CS3000 and COBE Spectra, are based on continuous-flow principles. These machines have complicated centrifugal separation chambers which can collect one specific blood component with high purity from a donor and return the other components to the donor. Other blood cell separators utilize a batch processing method and discontinuous flow, eg, the Haemonetics V50plus and Mobile collection system. These machines fill the separation chamber, collect the desired product, and then return the processed blood to the donor.

In some cases, density gradient solutions are used to separate a specific layer of cells. A solution, like Ficoll or Percoll, with a mass density between the density of the cells that are to be collected and the other cells, is added to the blood product.

3.2. Countercurrent Separation and Elutriation

The process known as elutriation in cell separation is a refined method for separation of cells having close mass densities. Cells can be separated by making use of differences in the critical velocity of cells. If the mass densities of two cells are identical, but the sizes are different, then the larger particle has a higher critical velocity than the smaller one.

According to Newton's second law, the sum of the forces on a particle, ie, one spherical cell in plasma, should equal its mass, m_{p}, times the acceleration of the cell or particle, a_{p}:

$$F_c - F_D - F_B = m_p a_p \qquad (1)$$

$$-F_g + \mathrm{F}_D + F_B = m_p a_p$$

where F_{g} (gravity) and F_{c} (centripetal) are forces on the cell, F_{B} (buoyant) and F_{D} (drag) are forces by the fluid on the surface of the cell. After a brief transient period, the cell falls with a constant settling velocity. For a fast rotating system, equation 1 reduces to

$$F_c - F_D - F_B = 0 \qquad (2)$$

If the particle is at a given radius from the center of rotation, the plasma now has to apply an inward drag force, F_D, on the cell to maintain the position of the particle:

$$F_D = F_c + F_B \qquad (3)$$

When this inward drag force, F_D, is exceeded by the plasma, the particle moves inward with the plasma. The inward velocity the plasma needs to exceed in order to drag the particle inward is called the critical velocity, U_{cr}, of the particle:

$$U_{cr} = \frac{2r_p^2}{9} \frac{\left(\rho_p - \rho_f\right)\omega^2 R}{\mu_f \phi(\mathrm{C})} \qquad (4)$$

U_{cr} in m/s is critical velocity; r_p, radius (size) of the particle; ρ_p, mass density of the particle; ρ_f, fluid mass density; ω, rotational velocity; R, position of the particle relative to the center of rotation; μ_f, viscosity of the fluid; and $\varphi(C)$, a function of the concentration of particles in the fluid.

Cell separation techniques that use an inward flow component are referred to as countercurrent separation techniques. The concept of countercurrent separation is complicated by biological variations of all parameters in equation 4.

The two principal applications of countercurrent flow are found in the Beckman elutriators and the Haemonetics apheresis equipment. The Beckman elutriators are capable of very specific cell separation of small batches of cells. The Haemonetics surge technique can separate platelets and lymphocytes from four liters of donor blood in one hour and forty minutes.

3.3. Beckman Elutriation Method

The Beckman elutriation method uses a chamber designed so that the centrifugal effect of the radial inward fluid flow is constant (Fig. 3). The separation chambers are made of transparent epoxy resin which facilitates observation of the movements of the cell boundary in strobe light illumination. This enables detection of the radius at which the cells are separating. When a mixture of cells, eg, mononuclear white cells, enters the chamber, separation can be achieved by fine tuning centrifuge speed and inward fluid flow to the specific cell group. This is a laboratory method suitable for relatively small numbers of cells. Chambers are available in sizes to handle $2 - 3 \times 10^8$, $1 - 2 \times 10^9$, and 1×10^{10} cells. The Beckman chambers can be applied to collect mononuclear cells from bone marrow aspirates.

3.4. Haemonetics Bowl Technology

Haemonetics disposable bowl technology has evolved from the original plasma separation chamber. The two principal shapes of bowls are the Latham bowl and the blow-molded bowl (Fig. 4).

Haemonetics' apheresis technology utilizes a discontinuous flow method, eg, countercurrent separation, to collect blood components such as plasma, single-donor platelets, lymphocytes, and stem cells. Anticoagulated blood from a donor enters the bowl via the inlet port and feed tube, as shown in Figure 5. At the end of the feed tube, the blood meets the base of the bowl and fluid is accelerated to the angular velocity of the bowl, ie, ω = 4800 rpm (540 rad/s). As a result of the centripetal force, blood migrates into the separation chamber, ie, the space between the body and outer core. In this separation chamber, blood separates into layers according to the mass density of the components. When the separation chamber is full, plasma is forced out of the separation chamber into the upper assembly where it contacts the effluent tube that is not rotating. The bowl has a unique rotating seal which maintains sterility of the bowl contents while allowing for rotation of the bowl. Plasma leaves the bowl through the effluent tube and outlet port into the effluent line, which leads to the collection bags.

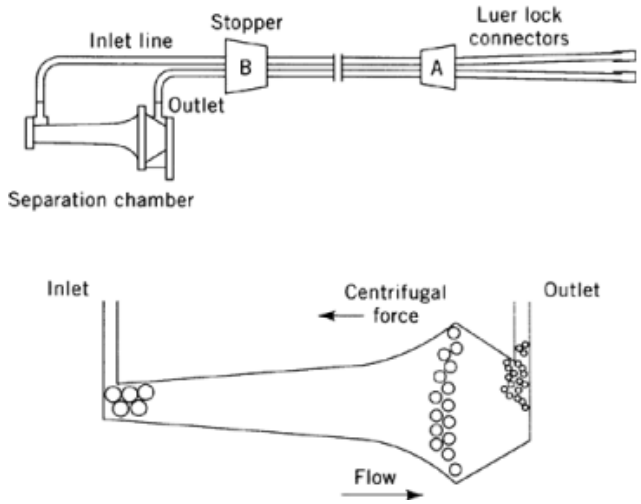

Fig. 3. Beckman elutriation chamber.

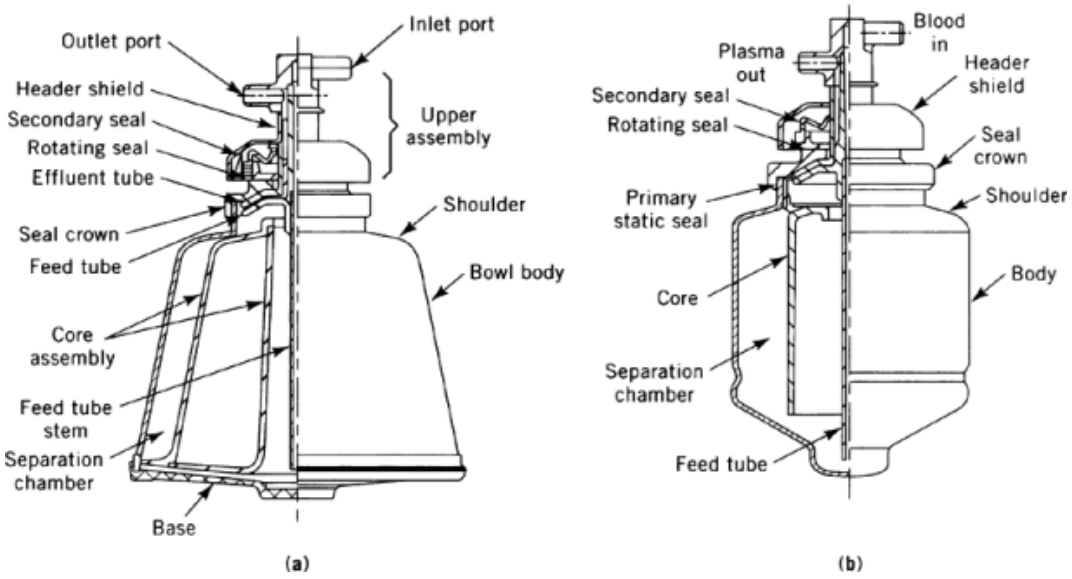

Fig. 4. Haemonetics disposable bowls: (**a**) Latham bowl, and (**b**) blow-molded bowl.

A small (25-kg), portable apheresis system, available in 1993, is designed to meet a wide variety of blood cell separation needs. The role of the apheresis system is to control the behavior, separation, and collection of blood components from the bowl while maintaining maximum donor safety. The system controls the flow rates of blood and components through variable pump speeds. It directs the flow of components out of the bowl, by fully automatic opening and closing of valves based on the output of the system sensors. The system monitors the separation of blood components in the bowl by an optics system that aims at the shoulder of the bowl. A sensor on the effluent line monitors the flow of components out of the bowl.

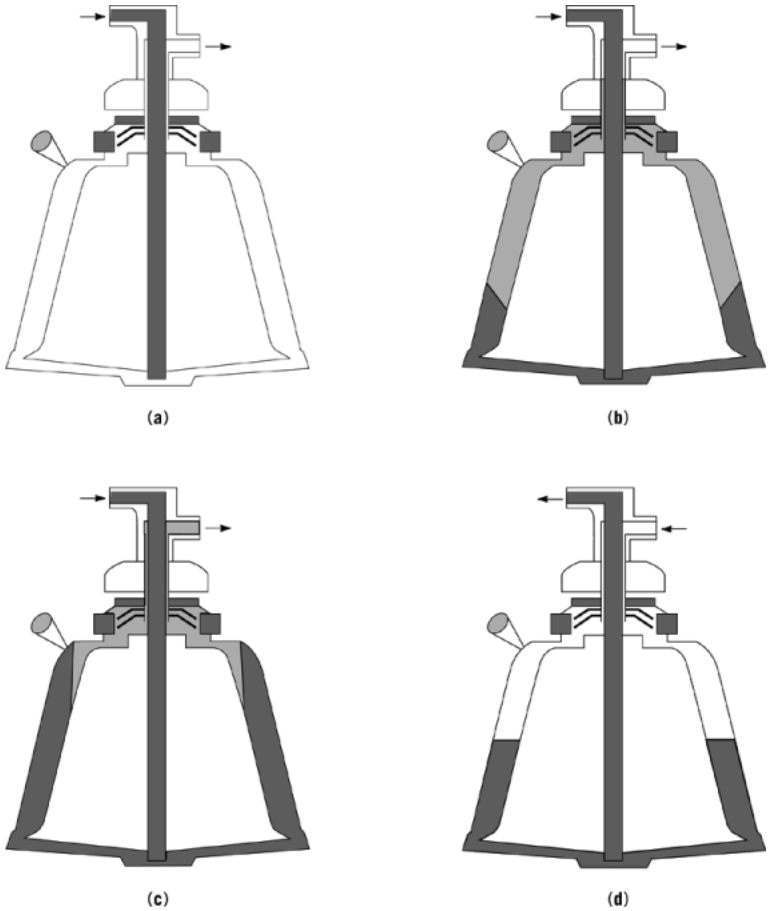

Fig. 5. Separation in Latham bowl: (**a**) whole blood is pumped down the feed tube and enters bowl at bottom; (**b**) centrifugal force spins denser cellular components outside, leaving plasma or platelet-rich plasma (PRP) in inner band; (**c**) when bowl is full, plasma flows out effluent tube, followed by platelets and then leukocytes, until bowl is almost completely full of red cells; (**d**) after draw is completed, bowl stops spinning and uncollected components are pumped through the feed tube and returned to donor.

The special design of the Latham bowl allows for a specific blood cell separation known as SURGE. This technique makes use of the principle of critical velocity. The Latham bowl is filled until the buffy coat, ie, layer of platelets and white cells, moves in front of the bowl optics. At this point the machine starts to recirculate plasma through the bowl at increasing rates. The smallest particles, ie, platelets, are the first to leave the bowl. Their high number causes the effluent line to turn foggy. The optical density of the fluid in the effluent line is monitored by the line sensor. A special algorithm then determines when to open and close the appropriate valves, as well as the optimum recirculation rate.

3.5. Filtration

Filtration (qv) is applied in blood cell separation to remove leukocytes from red blood cell (RBC) and platelet concentrates. Centrifugational blood cell separators do not reduce white blood cells (WBC) in red cell and platelet products sufficiently to avoid clinical complications such as GvHD and alloimmunization.

A post-apheresis filtration step is needed to further reduce the WBC load. Modern filters are capable of a 3-log reduction in white cell contamination of the blood product, eg, apheresis single-donor platelet units having a typical white cell contamination of5×10^8 white cells in 4×10^{11} platelets can be reduced to a 5×10^5 white cell contamination, a sufficiently low number to avoid severe transfusion reactions.

3.6. Filter Design

Modern leukocyte-reduction filters have become highly efficient as a result of careful filter design and advanced biomaterials. The binding of leukocytes to the filter media is weak, and hence the flow of blood components through the filter must be well controlled. Effects, such as channeling and bypass, are detrimental to the quality of the product. General design considerations include high flow rate through the filter, low retention volume, and hydrophilic filter media that does not require priming prior to filtration. The filter should also give a high yield of the source product, and loss of platelets or red cells in the filter as a result of either adhesion or retention volume should be minimal.

Two types of leuko-reduction filters are applied in blood cell separation: those for filtering red cells and those for platelet filtration. Filters designed for use with RBCs consist of two filtration layers: an upstream screen filter for trapping large particles and microaggregates, and a downstream adsorption filter for leukocyte reduction. The filters for platelet concentrates have only the adsorption filter. The two principal filter designs commercially available (ca 1993) are a relatively flat, large diameter disk-shaped filter, ie, the RC and PL filters of Pall Corp., and filters having a relatively small cross-sectional area but greater depth, eg, the SepaCell filters of Asahi Corp.

The white cell adsorption filter layer is typically of a nonwoven fiber design. The biomaterials of the fiber media are surface modified to obtain an optimal avidity and selectivity for the different blood cells. Materials used include polyesters, eg, poly(ethylene terephthalate) and poly(butylene terephthalate), cellulose acetate, methacrylate, polyamides, and polyacrylonitrile. Filter materials are not cell specific and do not provide for specific filtration of lymphocytes out of the blood product rather than all leukocytes.

Mechanisms of binding leukocytes to filter fibers are not yet fully understood. The longer a cell is in contact with the material, the more likely it is to attach to the filter. Therefore, too high a flow rate of blood product through the filter can impair performance. Cells that have attached to the filter can be detached if their critical shear force is exceeded. This can occur owing to increased local flow rates as a result of channeling; channeling may be induced by trapped air bubbles in the filter as a result of ineffective priming of the filter. The need for high flow rates also can impair peak performance of the filters, eg, in urgent bedside filtration.

Leuko-reduction can be performed at the time of collection by apheresis in the blood lab or at the patient's bedside. Economic, quality assurance, logistic, clinical, and liability considerations play a role in this. Leukocyte reduction filters are quite expensive, and leukocyte reduction may not be essential in all cases of transfusion.

3.7. Mechanisms of Leukocyte Adsorption

The exact mechanism of leukocyte adhesion to filter media is not yet fully understood. Multiple mechanisms simultaneously contribute to the adhesion of cells to biomaterials, however, physical and biological mechanisms have been distinguished. Physical mechanisms include barrier phenomenon, surface tension, and electrostatic charge; biological mechanisms include cell activation and cell to cell binding.

3.8. Barrier Phenomenon

In red cell filtration, the blood first comes into contact with a screen filter. This screen filter, generally a 7–10-μm filter, does not allow microaggregate debris through. As the blood product passes through the deeper layer of

the filter, the barrier phenomenon continues as the fiber density increases. As the path becomes more and more tortuous the cells are more likely to be trapped in the filter.

3.9. Surface Tension

Interfacial surface tension between fluid and filter media is considered to play a role in the adhesion of blood cells to synthetic fibers. Interfacial tension is a result of the interaction between the surface tension of the fluid and the filter media. Direct experimental evidence has shown that varying this interfacial tension influences the adhesion of blood cells to biomaterials. The viscosity of the blood product is important in the shear forces of the fluid to the attached cells; viscosity of a red cell concentrate is at least 500 times that of a platelet concentrate. This has a considerable effect on the shear and flow rates through the filter. The surface stickiness plays a role in the critical shear force for detachment of adhered blood cells.

3.10. Electrostatic Charge Density

Red blood cells, platelets, and white blood cells have a net negative surface charge at physiologic pH. The charge density per unit of cell surface area is different for these three cell lines. It is suspected that white cells carry the highest net negative charge density; therefore, filter media having the correct net positive charge is expected to selectively remove white cells from the filtered blood products.

3.11. Cell Activation

Several studies have shown that platelets and white cells undergo shape changes when adhering to filter media. The cells are activated by contact with the filter media and form pseudopods which attach to the filter media. The cells' membranes may need a certain degree of viability to be able to actively attach to the filter media. When white cells are treated with metabolic inhibitors, the capability of leukocyte reduction by the filter is reduced.

3.12. Cell Adhesion

The membranes of leukocytes and platelets contain a variety of components that promote cell-surface contact. Although numerous cell-surface molecules are likely to play a role in cell-surface adhesion, the group of selectins are of particular interest to research on this subject. Selectins are molecules that are known to promote leukocyte–platelet adhesion. However, selectin-based models have not been able to account for the fact that platelets are allowed to pass through the filter and leukocytes are not.

3.13. Cell–Cell Interactions

Older generations of leukocyte filters depended partly on the formation of platelet–leukocyte–thrombin formations. It is not clear whether this mechanism plays a role in third-generation filters.

3.14. Emerging Cell Specific Technologies

A number of cell specific technologies for cell separation are emerging. Cell specific typing through surface antigen marking is possible. The feasibility of separating two subgroups from white blood cell concentrates is being investigated; ie, stem cells, which are marked by the CD34 antigen, and lymphokine activated killer cells (LAK) (CD8). Purified stem cells can be used for cancer therapy (see Chemotherapeutics, anticancer), but also for curing various hematologic genetic diseases through DNA engineering of the purified stem cells (see Genetic engineering). The LAK cells are used to treat immune diseases.

Technologies to purify cells from white cell concentrates are in the research stage. Principles used include antibodies covalently bound to a surface, antibody-coated microbeads in a column, magnetic microparticles that have been coated with antibodies, and hollow fibers that have been coated with antibodies.

4. Regulations, Storage, and Shipment

Blood transfusion is highly regulated worldwide by government institutions, such as the USFDA, and through associations of blood banks, such as the American Association of Blood Banks (AABB). Strict regulations on good manufacturing practices (GMP) have been established to ensure maximum safety of the transfused products.

Each blood component has specific storage requirements in terms of optimal temperature, additives, expiration, and storage containers. Red blood cells (RBC) from whole blood, provided in 200 mL units, have an expiration of 42 days. Frozen, deglycerolized RBC, in 170 mL containers, and washed red cells, in 200 mL containers, both expire 24 hours after thawing and washing, respectively; leukocyte-reduced RBC, in 200 mL containers, are viable for 24 hours.

For optimal functionality, platelets require a stable and well-balanced pH, gas exchange, ambient temperature, and gentle agitation. Special plastics have been developed for optimal storage of platelets.

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