2. Apheresis: Definitions, Descriptions, and Developments

2

Apheresis: Definitions; Descriptions, and Developments

Apheresis is a procedure in which blood is separated into its basic components (red cells, white cells, platelets, and plasma), and one or more of these is selectively removed from the blood. It is applied therapeutically for the purpose of curing, alleviating, or treating a disease and/or its symptoms. The procedure is usually accomplished by removing venous whole blood from the body, separating the blood into cellular and noncellular (plasma) parts or "fractions," and returning the cellular fraction to the patient **(59,86). Just as with kidney dialysis, blood flows from a patient to a machine** where it is treated and then returned to the patient by way of an extracorporeal (i.e., outside the body) blood tubing set **(39). ***

In simplest terms, apheresis involves separating "bad blood" from good. Blood comprises four basic components: red cells, white cells, platelets, and plasma. A typical adult male has **3 trillion red cells in the blood.** The red cells deliver oxygen throughout the body and carry carbon dioxide back to the lungs, where it is exhaled. For every 800 red cells, the blood contains about 1 white cell. The several types of white cells (leukocytes) play key roles in the immunological defense system (lymphocytes), fight infections (granulocytes), and respond to foreign materials. Platelets, of which there are about 1 for every 20 blood cells, are spherical or oval bodies that help the blood to clot. Lastly, plasma, which contains large quantities of proteins, ions, and organic and inorganic molecules, makes up about 55 percent of blood volume, and is the straw-colored, fluid portion of circulating blood. The rationale for performing apheresis is to remove one or more of these components of blood that conceivably contain specific pathogenic substances linked to a patient's disease process (2).

A variety of diseases have been associated with abnormal proteins or blood components in the circulation, which are believed to initiate or aggravate the disease condition. Apheresis typically has been used in diseases involving three main types of abnormal levels of blood components: plasma protein, antibodies, and immune complexes.

Protein-related diseases involve either excessive levels of proteins in plasma (e.g., the macroglobulins in Waldenstrom's syndrome) or excessive levels of other substances which are "carried" in the blood by the plasma proteins (e.g., thyroid hormone in thyrotoxicosis). The antibody-related diseases are often termed "autoimmune" diseases. Normally, antibodies are produced by the immune system to attack foreign substances ("antigens") such as bacteria. However, in autoimmune diseases, pathological antibodies are produced which attack the body's own normal tissue, such as kidney cells in glomerulonephritis or the nerve/muscle junction in myasthenia gravis. ***Immune complexes*** are antigen-antibody complexes that can be deposited in tissue. In immune-complex related diseases, such as rheumatoid arthritis, this deposition occurs and produces severe inflammation and tissue damage (117).

The therapeutic goal of apheresis is to decrease the levels (through removal) of these abnormal components in the circulating blood. Physicians reason that if they can properly identify and remove these problem substances, the disease process may be controlled and the patient's clinical condition should improve.

Unfortunately, the effects of apheresis are not well understood. For the most part, its benefits remain anecdotal and difficult to reproduce. Its effects are not generally believed to be curative; rather, they are usually of a temporary nature. Often the procedure is used in conjunction with other treatments, especially drug therapy, making it difficult to assess the effectiveness of

● In kidney dialysis, however, the dialysis device does not separate the blood's cellular and plasma components of blood, but rather removes only unwanted metabolizes and waste products from the blood (39).

apheresis therapy. The scientific and medical applications of apheresis and corresponding levels of efficacy and effectiveness gained from such treatment are discussed at length in chapter 3.

Apheresis can take several forms: plasmapheresis, plasma exchange, plasma perfusion, cytapheresis, lymphapheresis, and lymphoplasmapheresis. Strictly defined, pkrqdxmsis involves the removal of small amounts of plasma. The primary use of this procedure is in the collection of source plasma for subsequent processing into serum fractions, as has been traditionally found in blood banks and in the plasma collection industry.

The plasma separation process, however, has been increasingly used over the last decade for therapeutic uses. The therapeutic application most often includes two general techniques. In plasma ***exchange,*** a large volume (up to **5 liters) of plasma is removed and replaced by an equivalent volume of fluids** such as fresh frozen human plasma, a plasma substitute, or combinations of albumin, calcium, and normal saline, depending on the need of the individual patient. * ***Plasma perfusion*** refers to a multiphase separation technique in which the patient's plasma is first isolated from the cellular elements and subsequently passed through a filtration medium (either adsorptive columns or membranes) to remove unwanted plasma components. The filtered plasma is then returned to the patient along with the cells **(39,108). Only recently has equipment for this technique been approved for general therapeutic use by the Food and Drug Administration (FDA) (see "Equipment Technology" section later in this chapter for a more complete discussion of plasma perfusion).**

Another form of therapeutic apheresis is cy*tapheresis,* the selective removal of specific blood cells (red cells, white cells, and/or platelets). Cytapheresis is usually subdivided according to ***plateletapheresis*** (the reduction of abnormally high levels of platelets), ***leukapheresis*** (the reduction of excess white cells, as in leukemia), and ***erythrocytapheresis*** **(the** removal of red cells) **(105). Cytapheresis can also include *lymphapheresis,*** the removal of lymphocytes (certain white cells) without depletion of plasma components, making any plasma replacement, therefore, unnecessary. ***Lymphoplasmapheresis*** is a combination of lymphapheresis and plasmapheresis: the removal of both lymphocytes and plasma, usually during a single procedure, and requiring the use of replacement fluids.

There are different types of hardware used for performing apheresis. One is a centrifugal type machine that spins the blood in a chamber and uses centrifugal force to separate the heavier parts of the blood from the lighter ones. The filter type uses a flat sheet or hollow fiber porous membrane to separate the larger blood components from the smaller. This type is only capable of removing plasma from the cellular portion of the blood: plasma and plasma proteins easily pass through the pores in the membrane but the red cells, white cells, platelets, and large protein molecules are too large to pass. Thus, the filter-type device can only perform plasmapheresis. Although the centrifugal type of device is more versatile, the filter type has fewer moving parts and is easier to operate (39).

*It is important to note that some researchers also make a distinction between ***plasma exchange*** **and** ***plasma infusion.*** In the former case, plasma is removed and replaced by a **colloid** solution, commonly albumin, fresh frozen plasma, or simple donor plasma. **Al**though the plasma replacement in early cases was initiated only for purposes of expansion of the blood vessel "intravascular" volume, later authors suggested that the administration of fresh frozen plasma had an independent therapeutic effect. This **led** some investigators to administer it without **apheresis**; this is described in the literature as plasma infusion.

HISTORICAL DEVELOPMENT

The idea of apheresis (from the Greek, ***aphairesis,*** meaning "taking away") first originated in 1914 with a group headed by John J. Abel at Johns Hopkins Medical School **(l),** which attempted to develop an artificial kidney in dogs. In the course of this work, they investigated the effect "of the repeated removal of considerable quantities of blood, replacing the plasma by Locke's solution," and infused the mixture back into the dogs. They showed that dogs were able to tolerate the ex-

change of substantial volumes of plasma and coined the term "plasmapheresis" to describe the procedure. They suggested that "if this method can be employed without harmful consequences it is probable that it could be applied in a bolder manner in a greater variety of morbid states than the time honored but often debatable" medical practice of bloodletting **(67).**

For 30 years, plasmapheresis was used mainly in experimental animals, to study the metabolism of plasma proteins (67). The possibility of human plasmapheresis was first considered during World War II as a means of meeting the increased demand for plasma. A trial conducted in 1944 demonstrated the feasibility of weekly plasma donations. Over the last 20 years, the collection and processing of donor plasma has evolved into a major industry as the demand for plasma fractions, such as albumin, has increased (108).

The first successful therapeutic use of plasmapheresis was reported in the late 1950's in the management of macroglobulinemia (thickened blood due to the accumulation of proteins) and multiple myeloma, a malignant tumor of the bone marrow. During the next few years, reports appeared on the application of plasmapheresis to several other diseases, including rheumatoid arthritis in which a circulating "plasma factor" was implicated. In these treatments, a small volume of plasma was removed and replaced only with isotonic saline solution. The procedure was slow and limited by the tendency to deplete all plasma proteins (both beneficial and harmful) if conducted too often (108).

Over the past 10 years, however, several types of cell separators have been developed which can efficiently separate large quantities of red cells, white cells, platelets, and plasma either continuously or on an intermittent basis. In the late 1960's, International Business Machines (IBM) Corp. developed the first cell separator in a collaborative effort with the National Cancer Institute. A second type of device was subsequently developed commercially by Haemonetics, Corp., of Massachusetts (80,108).

During the early 1970's cell separators were mainly used by blood banks to harvest white cells and platelets, and to collect plasma and plasma fractions intended for transfusions or research. But as apheresis evolved more toward a therapeutic application in the mid 1970's, the equipment-embodied cell-separator technology was easily and rapidly modified for therapeutic use.

The medical literature has reflected this burgeoning interest in therapeutic apheresis. In 1981, there were approximately four times as many articles on the subject appearing in lndex Medicus as there were in the 1970's (85). To date, apheresis has been used in the treatment of over 75 diseases, and an additional 41 diseases have been identified as possible candidates for this therapy (22,117). Table 1 presents a listing of diseases in which the use of therapeutic apheresis has been reported in the medical literature.

The growing interest in therapeutic apheresis is further exemplified by the emergence of professional societies, scientific meetings, and journals devoted entirely to this subject. The membership in the American Society for Apheresis has increased dramatically, for example, and the journals, ***Plasma Therapy and Transfusion Technology*** and ***Journal of Clinical Apheresis*** have **initiated publication only within the last 5 years (43,49,145).**

Table I.—Reported Use of Therapeutic Apheresis

- Acute necrotizing hemorrhagic encephalomyelitis
- Acute disseminated encephalomyelitis
- Acute post-streptococcal glomerulonephritis
- Acute rheumatic fever
- Addison's disease
- Adenocarcinoma of the colon
- Adenocarcinoma of the breast
- Allergic granulomatosis and angiitis
- Amyloidosis
- Amyotrophic lateral sclerosis (ALS)
- Ankylosing spondylitis
- Aplastic anemia
- Atopic dermatitis
- Atrophic gastritis type A
- Autoimmune infertility & gonadal insufficiency
- Autoimmune hemolytic anemia (AIHA)
- Autoimmune hypogammaglobulinemia
- Autoimmune neutropenia
- Behcet's syndrome
- Bone marrow transplant
- Bronchial asthma
- Bronchogenic carcinoma
- Bullous pemphigoid
- Cardiac allograft rejection
- Chronic membranoproliferative hypocomplementemic glomerulonephritis
- Chronic active hepatitis
- Circulating anticoagulant (Anti-Factor VIII)
- Cold agglutinins
- Colon carcinoma
- Crohn's disease
- Cryogenic fibrosing alveolitis
- Cryoglobulinemia
- Cutaneous vasculitis
- Dermatitis herpetiformis
- Dermatomyositis
- Discoid lupus erythematosus
- Disseminated intravascular coagulation (DIC)
- Dressier's syndrome
- Eaton-Lambert syndrome
- Endomyocardial fibrosis
- Erythema multiform
- Fabry's disease
- Felty's syndrome
- Gastric carcinoma
- Gaucher's disease
- Giant cell arteritis
- Glomerulonephritis in subacute bacterial endocarditis
- Goodpasture's syndrome
- Graft versus host disease
- Graves' disease
- Graves' ophthalmopathy
- Guillain-Barre syndrome
  - Acute
  - Chronic
  - Relapsing
- Hashimoto's thyroiditis
- Hemolytic uremic syndrome
- Henoch-Schonlein purpura
- Hepatic coma
- Herpes gestations
- Hodgkins disease
- Hypercholesterolemia
- Hyperglobulinemic purpura
- Hypersensitivity pneumonitis
- Hypersensitivity angiitis
- Hypertension
- Hypertriglyceridemia
- Hyperviscosity syndrome
- Idiopathic membranous glomerulopathy
- Idiopathic thrombocytopenic purpura (ITP)
- Idiopathic hypoparathyroidism
- Insulin resistant diabetes mellitus due to anti-receptor antibody
- Juvenile onset diabetes mellitus
- Lipoid nephrosis
- Lymphomas
- Malignant melonoma
- Mixed connective tissue disease
- Multiple sclerosis
- Multiple myeloma
- Myasthenia gravis
- Necrotizing cutaneous angitis
- Neuroblastoma
- Other neoplasms
- Pemphigus vulgaris
- Pernicious anemia
- Poisoning or overdose (paraquat, mushroom, digitalis)
- Polyarteritis nodosa
- Polymyositis
- Post-transfusion purpura
- Primary cardiomyopathy
- Primary biliary cirrhosis
- Proliferative/membranoproliferative glomerulonephritis
- Psoriasis
- Pure red cell aplasia
- Rapidly progressive glomerulonephritis
- Raynaud's disease
- Refsum's syndrome
- Reiter's disease
- Renal allograft rejection
- Reye's syndrome
- Rhesus iso-immunization
- Rheumatoid arthritis
- Sarcoidosis
- Scleroderma
- Sjogren's syndrome
- Subacute bacterial endocarditis
- Systemic lupus erythematosus (SLE)
- Takayasu's arteritis
- Thrombotic thrombocytopenic purpura (ITP)
- Thyroid storm
- Ulcerative colitis
- Viral hepatitis
- Waldenstrom's macroglobulinemia
- Wegener's granulomatosis
- White cell isoantibodies

SOURCE: Off Ice of Technology **Assessment,** 19S3.

THE SCIENTIFIC AND MEDICAL BASIS FOR USE'

For therapeutic use, apheresis technology came along at an opportune time—when there is a growing support for the theories that a large number of chronic conditions occur because the antibodies of the immune system, instead of attacking foreign substances as they are supposed to, attack the body's own tissues. This results in a build-up of so-called immune complexes, which are carried in the blood (34).

Indeed, many diseases that appear to respond to apheresis seem to have common elements: they reflect failures in the immune system, the body's defense network of sorts, which is designed to protect the individual against viruses, foreign cells, and some poisons. The cells of the immune system circulate in the blood and lymph systems and also reside in specialized tissues such as the thymus, spleen, and lymph nodes. There are two principle modes of immunity: humoral immunity and cell-mediated immunity. Humoral immunity is realized through antibodies, which are proteins produced by lymphocytes and which circulate in the blood system. They represent the major defense against bacterial infections. Cellular immunity is realized through lymphokines (also lymphocyte products) which are responsible for a variety of phenomena including influencing migration of inflammatory cells, allergic responses, dilation of the blood vessels, rejection of tissue grafts, and other foreign matter.

The foreign agents eliciting immune responses are called ***ant&ens,*** which may be circulating proteins or other types of molecules, or also substances on the surfaces of bacteria or foreign tissue. When individuals are exposed to an antigen, their lymphocytes respond by making antibodies specifically directed against the antigen. The antibodies have binding sites which attach to the antigen, and together they form aggregates called ***immune complexes.*** These complexes circulate in the bloodstream and are subsequently processed and removed from the body by cells located in the liver, spleen, and other organs. It is in this manner that foreign agents are eliminated.

The formation of immune complexes triggers many other reactions. One of these is activation of the ***complement system,*** a set of proteins found in the blood. Complement products can kill cells with antigens on them, such as bacteria. They also attract inflammatory cells to the area where the antigen-antibody reactions are taking place, and these cells assist in clearing the antigens.

Antigens also stimulate specific lymphocytes, ***Tlymphocytes,*** to proliferate and then differentiate. Some T lymphocytes differentiate into "helper cells" which assist the lymphocytes in making antibodies; some differentiate into "killer" lymphocytes which can kill foreign cells having antigen on their surface; and some cells differentiate into "suppressor cells" which regulate the immune response by inhibiting further antibody production against the specific antigen.

The exact nature and extent of the immune response depend on many factors: the type of antigen, its route of entry into the body, the genetic makeup and state of health of the host, the types of antibodies made, and the relative proportions of helper, killer, and suppressor cells generated. A fundamental property of an individual's immune system is that it distinguishes between the antigens on the body's own tissues and those on foreign agents. Unfortunately, this system occasionally breaks down, and individuals mount immune responses, most often antibody production, directed against their own tissues. The diseases that result from such a disorder are referred to as "autoimmune diseases. "

The cause and pathological development of autoimmune diseases are thought to be due to several mechanisms: ***inactivation reactions, cytotoxic reactions,*** immune complex deposition, ***anaphylaxis,*** and ***delayed hypersensitivity.*** These mechanisms are briefly discussed in appendix E.

[1]Unless otherwise noted, this section is condensed from Frost & Sullivan, Inc., *In-Vivo Hemodetoxification and Hemoprocessing Markets in the U. S., New* York, June 1981.

THE TREATMENT PROCESS

Until the advent of automated devices, the process of apheresis was exhausting and time-consuming, requiring 4 to 5 hours, for example, to remove about 1 quart of plasma. It was a tedious manual procedure in which the patient's blood was drawn one bag at a time, separated in a centrifuge so that the target components could be removed and the remaining blood returned to the patient before drawing another bag. Now, automated cell separators reduce the procedure to a simple, straightforward exchange which can be completed in 2 to 4 hours. The patient is connected to the cell separator, which draws the blood, separates the components, and returns the rest of the blood to the patient. The volume exchange for each procedure is calculated for each patient according to size and the type of treatment modality desired (73).

Organizational Settings and Staffing

Apheresis treatment is provided almost exclusively through large medical school hospitals and community/Red Cross blood banks. A few commercial, freestanding, independent centers have been established during the past 2 or 3 years; however, it appears that this trend maybe moderating.

Most of the existing therapeutic apheresis programs originally evolved in conjunction with the donor facilities at community and hospital blood banks. However, some of the larger institutions have since established independent hemapheresis units (which undertake and perform hemodialysis and other blood filtration procedures in addition to apheresis) that perform leukapheresis and plateletapheresis in addition to plasma exchange.

The hemapheresis center is normally staffed by nurses with special (usually "on-the-job") training in the operation of the cell separator equipment, administration of replacement fluids, circulatory access techniques, and the treatment of apheresis complications. The operation of the unit is directed by a physician, often a hematologist.

In most centers the actual procedure is conducted by one or two apheresis nurses. Usually a physician (who is often the center director) is required to be immediately available in the event that complications should develop. In many of the smaller facilities the supervising physician is in direct attendance during the procedure, while in the larger apheresis centers he or she is generally on call within the unit (49,108).

Frequency, Intensity, and Duration of Blood Component Exchange

The volume and frequency of blood component exchange depend to a large degree on the disease being treated as well as the individual patient response. To date, temporal considerations have been more influenced by factors such as circulatory access and scheduling than by uniform protocols, because the metabolism, kinetics, and pathogenicity of the abnormal blood component constituents removed by apheresis have not been largely established (144). Therapy regimes that have evolved from clinical studies vary as a result. Frequency of treatment ranges from an average of 3 procedures in the management of myeloma to approximately **16 treatments per year for patients with chronic myasthenia gravis (though severely debilitating rheumatoid arthritis may require up to 30 treatments in the first year, with that number decreasing thereafter (47). The average for all reported diseases treated by apheresis ranges from approximately 5 to 15 treatments per year per patient, at a volume of 3.2 liters (the range is 2.0 to 4.5 liters per treatment) (108).**

A survey of hospital and community blood banks by Scoville Associates (108) indicated, however, an average of only 5.6 treatments per patient during 1980. Average volume per exchange was 2.8 liters (1.5 to 3.5 liters). The difference in treatment schedules was hypothesized to stem from several factors. For example, the hospital and blood bank averages included schedules for just 30 different disorders, many of which were treated on an acute basis only. Also, a major objective in acute treatment settings is to obtain rapid patient response, and several centers reported that they usually terminated apheresis after three to four procedures if improvement is not apparent.

Circulatory Access and Replacement Fluids

The initial step in the apheresis procedure involves the removal of whole blood from the patient for subsequent separation. Blood vessel access is not (because of relative infrequency) as critical in this procedure as it is, for example, in chronic hemodialysis in end-stage renal disease applications. The preferred access site is a simple puncture into the vein at the elbow. Such access is adequate for most patients even with extended series of exchanges.

The cellular elements and replacement fluids are normally returned to a vein in the other arm. Other return sites include the femoral vein, forearm, or through a small vein in the hand or foot. Sometimes repeated apheresis treatment requires surgeons or other qualified staff to make a shunt or fistula, a sort of permanent "tap," between an artery and a vein to give them ready access to the circulatory system. Clotting and site infections can be significant complications in the use of such taps.

Crystalloid solutions (saline, Ringer's solution, Hartman's solution) are normally used routinely as replacement fluid in small volume apheresis procedures. These involve removal of 1 to 2 liters of plasma every 2 to **3** weeks as in some cases of hyperviscosity syndrome. Crystalloid solutions have the advantage of low cost. Larger volume exchanges run the risk of protein depletion, and as a rule, require the use of colloid replacement fluids such as albumin, fresh frozen plasma (FFP), or plasma protein fraction (PPF). Guidelines have been established by FDA for safe levels of plasma donation without protein replacement in the average size adult.

The typical plasma exchange schedule, however, involves the removal of between 2 to 3 liters of plasma at a frequency of two to four times per week, and protein replacement is routinely utilized in these cases. In general, little is known about the correlation between specific disease states and the effectiveness of various replacement fluids.

Fluid volume removal is normally replaced on an equal basis. Since continued exchange will remove the replacement fluids as well as the patient's own plasma, many centers are now beginning to use a technique whereby saline or dextran is administered at the beginning of the procedure, and the protein replacement portion (FFP, PPF, or albumin) is infused toward the end of the exchange, thus saving some depletion of the more expensive colloid solutions. This proportion of protein solution to total replacement fluid generally ranges between **30** to **50** percent (2,108).

Drug Therapy Used With Apheresis

Apheresis used alone has often provided only transient results because cells making deleterious antibodies may not be affected. In fact, a "rebound effect" can sometimes occur when apheresis is used by itself, where posttherapy antibody levels are even higher than initial levels. Apheresis has, as a result, often been more effective when used in combination with immunosuppressive, cytotoxic, and anti-inflammatory drugs. Examples of these include cyclophosphamide, azathioprine, and steroids (e.g., prednisone). In specific diseases these drugs may be used individually, but they are often administered together.

Steroids have many complex physiological effects, and the effects of those that are responsible for suppressing inflammation, immune responses, and symptoms of autoimmune diseases are not completely understood. The basis of action of cytotoxic drugs is that they kill lymphocytes, and thus antibody production is decreased.

With corresponding drug therapy, then, the low levels of circulating antibodies and immune complexes rapidly achieved by apheresis may be maintained, since the rebound effect and the production of antibodies by lymphocytes are inhibited by the drugs. Other internal repair mechanisms can then intercede, correcting or repairing damage induced by the immune complexes or antibodies. For example, in myasthenia gravis, lowering the concentrations of antibodies allows new muscle membrane proteins to be synthesized. Removal of circulating immune complexes may also "desaturate" the immune complex clearing mechanisms in lymphoid tissues and allow them to function better.

For some diseases, apheresis, in combination with the drugs, has been claimed to result in complete remission. For others, long-term benefits have been reported. On the other hand, some diseases thought to be autoimmune have not been improved with apheresis. Ultimately, the successful treatment of autoimmune diseases will hopefully rely on more specific therapies, because these drugs are not without complications and can deplete sets of cells required for other vital bodily functions (42). Chapter 3 more fully discusses scientific and medical issues of apheresis.

EQUIPMENT TECHNOLOGY

Centrifugal Systems

Approximatelys percent of therapeutic apheresis procedures are performed manually by removing whole blood, spinning it down in a stationary centrifuge and returning the cellular components to the patient as is done in source plasma collection. Manual apheresis has the advantage of requiring relatively inexpensive equipment. However, its use is limited to the removal of small volumes of plasma (1.0 liter or less) due to the inconvenience and additional time requirements as compared to automated techniques. The rate of plasma removal using manual procedures runs approximately **2.5** hours per liter as compared to 1.2 hours per liter for automated cell separation equipment. Also, the use of a "non-closed" (manual) system runs a higher risk of infection and presents the possibility of returning the wrong red cells to the patient.

Most apheresis procedures are earned out using automated centrifuge equipment. There are two basic types of automated centrifuge devices currently in use for apheresis: the intermittent flow centrifuge (IFC) and the continuous flow centrifuge (CFC). Both systems provide a significant advantage over manual apheresis because large volumes of plasma maybe processed quickly with less risk to the patient. IFC devices are manufactured and sold by Haemonetics Corp. The Haemonetics Model **30** is used for a majority of the therapeutic plasma exchange procedures performed in the United States. This equipment was originally designed for the collection of leukocytes and platelets, but has been found to be effective for large-scale plasma exchange, lymphoplasmapheresis, and lyrnphapheresis as well (57,108).

Generally, in the IFC system, blood is drawn from a blood vessel in the arm and pumped through tubing into a disposable bowl placed in the well of the centrifuge. Several lines are also connected to the bowl leading to collection bags. Anticoagulant is introduced into the lines to be mixed with the donor/patient blood. As centrifugation begins, plasma is the first fraction of blood to be separated and collected into a container. Platelets and white cells are separated later in the process and are then diverted to other containers. When the process is completed, the pump action reverses and the red cells remaining in the bowls are reinfused into the patient via a blood vessel in the other arm. When the bowl is empty the whole procedure is repeated according to the effect desired **(42).**

The first CFC device, developed in the late 1960's by IBM in conjunction with the National Cancer Institute, involved a rotating seal which enabled the continuous infusion of whole blood and removal of separated components from a rotating centrifuge bowl. This basic CFC design was commercialized by IBM as the Model **2990** and by American Instrument Co. (now a division of Travenol Labs) as the Aminco Centrifuge. A few of these devices are still in use throughout the United States, but most have been replaced by the Haemonetics **30** or the second generation IBM Model **2997,** which employs a ring-shaped separation channel in place of the previous centrifuge bowl (108}.

Fenwal Laboratories (Division of Travenol Labs) has developed a series of CFC instruments (CS-3000 and Centrifuge II) in which the blood and separated components pass to and from the

separation chamber through continuous tubing, without the requirement of a rotating seal. A counter rotating mechanism is employed which enables the tubing to be continuously unwound without twisting or coiling (108).

The ***disposable*** equipment associated with apheresis varies according to the technique used. In the mechanical plasma separation application, disposable consist of tubing to connect the patient to the equipment and vice versa. A disposable bowl is fitted into the centrifuge and the separation takes place, then various bags are connected to the bowl to collect plasma and/or cellular components. Since the cellular components extracted during therapeutic apheresis are not intended for reuse in other patients, the disposable are simpler and less costly than those used in most blood banking operations (42).

Some new major developments in hardware are now undergoing clinical tests. These include adsorption columns and semipermeable membranes that function as molecular sieves.

Membrane Separation Devices

Membrane separation devices have evolved as parallel flow (or flat sheet) or hollow fiber configurations similar to those found in basic types of hemodialyzers. Membrane blood separators can only filter plasma from cellular components (as opposed to centrifugal systems that can also be used for specific cell separation (cytapheretic) applications as well as for plasma exchange). Membrane systems, however, are expected to allow simpler, more rapid and more precise treatment. They are currently being reviewed by FDA (see the "FDA Device Regulation" section of this chapter) for use in this country.

The ***disposable*** associated with membrane apheresis represent the heart of the plasma separation process. The plasma separation membrane replaces the centrifuge in this process. Tubing is used to form the extracorporeal circuit, very much as in dialysis **(42).**

Membrane disposable are expected to be initially priced higher than those required for centrifugal machines, but it should be noted that in Europe, especially in West Germany, many clinicians use Asahi-brand hollow fiber membranes in preference to centrifugal systems despite the higher costs. Membrane systems, in fact, are dominant in the European and Japanese markets, accounting for 70 to **80** percent of the procedures performed. If membrane systems become accepted in U.S. markets, manufacturing costs could decrease substantially to reflect economies of scale, although prices are not expected to approach those for similar membranes used for dialysis ($15 to **$25** per patient). Apheresis membranes will be initially more expensive because they are more delicate and their quality constraints will be more demanding in terms of pore size and wall thickness consistency (117).

Future Technological Directions

Current apheresis therapy most often entails plasma replacement, which is not only expensive but also removes normal as well as adverse plasma constituents. Therefore, future systems will likely emphasize more selective removal of undesirable components and return of the patient's own plasma, probably by one of the following techniques. (In most instances, however, the specific unwanted target components underlying the usefulness of plasma exchange have not yet been precisely identified.)

Cryoprecipitation.— Certain macromolecules in the plasma will precipitate (come out of suspension) when exposed to cold temperatures. When applied in conjunction with apheresis, the patient's plasma is circulated through a cold environment, where cryoprecipitation occurs. These precipitant are removed by filtration, and then the remaining plasma and cells are returned to the patient. Other macromolecules in addition to unwanted immune complexes are removed by this procedure. However, most normal plasma proteins, especially albumin, are retained. Parker-Hannifin Co.'s Cryomax system (see table 2) is likely to be the first selective entry.

Mechanical Double Filtration.—Another approach to avoiding the replacement of plasma in therapeutic apheresis is double filtration for

'This section is drawn from L. F., Rothschild, Unterberg, Towbin, 'Therapeutic Apheresis," New York, 1981.

Table 2.—Automated Blood Cell Separation Systems

Manufacturer	Models	Introduced	Approximate machine cost	Approximate disposables	Components separated	Membrane type
Continous-flow centrifuge						
Fenwal	CS-3000	1979	$32,000	$65-$80	Cells, plasma	None
(Travenol/Baxter)	Centrifuge II	1981	$19,700	$65-$80	Cells, plasma	None
IBM Biomedical	2997	1977	$31,000	$65-$60	Cells, plasma	None
Intermittent-flow centrifuge						
Haemonetics	30	1973	$21,600	$65-$80	Cells, plasma	None
	V-50	1980	$28,800	$30-$49	Cells, plasma	None
	PEX	1980	$25,600	$49 avg.	Cells, plasma	None
Continuous-flow membrane						
Cobe Laboratories	Centry TPE	March 1982	$30,000	$80-$90	Plasma only	Sheet
Parker-Hannifin	Cryomax	1983 (expected)	$30,000	$390	Plasma only	Hollow fiber
Fenwal (Travenol/Baxter)	PS-400	Late 1981 in Europe	$20,000	$75-$200	Plasma only	Hollow fiber
Organon-Teknika (Netherlands)	Curesis	NA	NA	NA	Plasma only	Hollow fiber
Asahi (Japan)	Plasmaflo@	(expected)	NA	$175-$400	Plasma only	Hollow fiber
Fresenius (West Germany)	Plasmaflux@	NA	NA	NA	Plasma only	Hollow fiber
Toray (Japan)	Plasmax	NA	NA	NA	Plasma only	Hollow fiber

[a]Disposables cost estimates are exclusive of other deposable items such as needles, saline bags, transfer pecks, and priming solutions which may also be used in conjunction with apheresis treatments.
NA - Not available.
SOURCES: L. F. Rothschild, Unterberg, Towbin, 1981; Friedman, American Red Cross, 19S2; Collins, Cobe Labs, 19S2; Ciuryla, Du Pent, 19S2.

albumin recovery. This type of system is essentially similar to the Cryomax approach, but the plasma fraction is not chilled to produce precipitation. After the plasma is separated from the cellular fractions by a membrane, it is passed through another membrane with smaller pores that allow only smaller proteins, especially albumin, to pass while retaining the larger macromolecules including immunoglobulins. The albumin fraction is then combined with the cellular fraction and returned to the patient. Albumin recovery systems are under investigation by several groups around the world.

Hemoperfusion.— This approach involves the passage of whole blood through an adsorption column (e.g., activated charcoal) to remove the unwanted substance(s) somewhat more selectively. This technique has been used primarily for detoxification in acute chemical or drug poisonings, and is being investigated for use in renal and liver failure. **It** offers desired speed in emergency cases, but for broader usage is not as promising as plasma perfusion (described below) due to unwanted cellular adherence to the columns and potential release of particles from columns.

Adsorptive Plasma Perfusion. -This technique should permit considerably greater selectivity in plasma component removal. It involves separation of plasma from cells, passage of the plasma through an adsorptive column (which specifically removes the unwanted substance), and return of the plasma and cells to the patient. Beneficial results in recurrent breast cancer treated with plasma exchange with on-line adsorptive column treatment have been recently claimed. Future development of adsorptive plasma perfusion may well involve columns containing monoclinal antibodies produced to specifically bind and, thus, selectively remove undesirable constituents.

Artificial Antibodies.—As previously discussed, antibodies are synthesized by lymphoid tissue to bind to and inactivate antigens (generally foreign substances). Antibodies are made to bind very selectively to specific antigens like a key in a lock. Unwanted plasma antibodies could be re-

moved by allowing them to bind to: 1) their natural antigenic "lock," which is held within a column ("antigenic columns"); or 2) an artificially produced antibody to the patient's normal and unwanted antibody, which is held within a column through which the plasma passes ("antibody column"), i.e., the unwanted antibody serves as an antigen to another manufactured antibody.

Artificial antibodies are currently produced for use in diagnostic tests using the immune response of goats or other animals especially for radioimmunoassays, a technique that allows an accurate measurement of biological and pharmacological substances in the bloodstream and other fluids of the body. Recent advances in gene splicing technology have given rise to monoclinal antibody or hybridoma (hybrid cell) techniques which allow the production of more specific antibodies at less cost than conventional procedures.

Based on current technology, economic factors may delay the development of monoclinal antibody columns for on-line plasma processing, except in certain diseases with only a few definable types of unwanted factors. Other diseases may require a constellation of distinct antigens or antibodies held within a column. Another potential problem for immunological adsorption columns concerns the quantity of unwanted substance to be removed. If, for example, large quantities of immune complexes must be removed, large quantities of antibodies would be needed in the columns. It is currently uncertain whether monoclonal production would be inexpensive enough to allow ***columns*** with large quantities of manufactured antibodies to be economically feasible.

FDA Device Regulation

FDA regulations currently governing centrifugal cell separators on the market only concern blood banking applications. The centrifugal apheresis devices have been classified into Class III (premarket approval or PMA) for use with donors in the preparation of blood products,[3] although data indicate many clinicians are using them for therapy. Machines introduced prior to the Medical Device Amendments in 1976 have "grandfathered" approval, while centrifugal machines introduced after 1976 have gained FDA premarket approval by being considered by FDA to be substantially equivalent to pre-1976 devices.

The membrane-based devices being developed, and mostly being tested in clinical trials, were not permitted to simply file a premarket notification with FDA. * They are considered essentially new devices for which investigational device exemptions (IDEs) are required. IDEs are granted with sufficient demonstration of safety, after which the clinical protocols can then proceed. Results of the clinical trials are used in filing for premarket approval. No attempts to reclassify separators as Class II devices, which would only require the manufacturers to meet certain product performance standards specifications, are being pursued at present. It has been speculated that the industry, on its own initiative in the future, could develop such standards for FDA approval (117).

In October **1981,** the Gastroenterology-Urology Device Section of FDA's General Medical Devices Panel reviewed the Cobe Centry TPE System for total plasma exchange and recommended approval of the device for therapeutic applications. On March **16, 1982,** FDA granted the premarket approval.

A second and third membrane apheresis PMA (Parker-Hannifin's Cryomax model and Asahi's Plasmaflo model) were reviewed and recommended for approval by FDA's General Medical Devices Panel in late **1982.** These models are expected to receive FDA's premarket approval and to be generally marketed in early **1983 (21).** In addition, there are currently in excess of **20** IDEs for conducting clinical investigations with apheresis membrane devices which are manufactured by five different manufacturers (39).

[3]21 CFR 864.9245.

● Sec. 510(k) of the 1976 Medical Device Amendments requires any distributor of a medical device intended to be marketed for the first time to file a notice with FDA at least 90 days in advance to permit the **agency** to decide whether the device is determined to be "substantially equivalent" to devices already on the market before the passage of the ***1976*** amendments or, if not found to be substantially equivalent, whether the device needs **premarket** approval to assure safety and efficacy.