

# **Scientific and Medical Aspects of Apheresis: Issues and Evidence**

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Various types of apheresis procedures have been performed on a clinical basis for many years, but the number of patients and types of diseases treated have risen significantly in the last 5 years. This increase is partially due to increased understanding of the disease and partially due to engineering advances in equipment technologies. By almost any standard, treatment by apheresis is still in relatively early stages of development—there are no ideal protocols based on a thorough understanding of reasons for its efficacy. Nevertheless, there is an increasing flow of clinical data, sometimes describing dramatic patient improvement, supporting the view that apheresis is a rapidly emerging technology with significant promise (117). Such evidence of treatment effectiveness<sup>\*</sup> is even today, however, often based on unsystematically collected data. Because of the

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<sup>\*</sup>**Effectiveness** is the health benefit as measured under average conditions of use. **Efficacy** is the health benefit as measured under controlled conditions such as those in a randomized clinical trial (104).

## METHODOLOGICAL ISSUES

An assessment of any medical technology depends, in part, on the development of a strategy for identifying technologies to be evaluated, and on the development of clear-cut standards for the quality of the evidence that should be considered (104,147). **Proper research methods, as a result, become essential to the evaluation of a technology. Careful and systematic investigations are the essential ingredients in establishing that observed effects are due to the medical intervention. Poorly and haphazardly conducted research studies are plagued with problems of validity and generalizability, and these same issues continue to hinder attempts to perform assessments based on such research (85).**

paucity of high-quality research, conclusions about the safety, efficacy, and effectiveness of apheresis are necessarily limited, although some tentative conclusions and directions for treatment can be discerned.

The present chapter analyzes the methodological problems in conducting apheresis research and examines available evidence of the safety, efficacy, and effectiveness of apheresis. Following a discussion of methodological issues, several major reviews of apheresis research will be summarized and evaluated. This chapter will further include the findings of a primary literature review and assessment of apheresis in the treatment of three diseases—namely, hemolytic uremic syndrome, acquired Factor-VIII inhibitor, and Guillain-Barré *syndrome*—where preliminary reports and evidence have been “promising” in utilizing apheresis as a therapeutic approach (57). (A full discussion of these findings can be found in apps. B, C, and D.) Present and future research directions for apheresis will be considered last.

To be valid, and to permit generalizations to be drawn, there must be clarity about what is being tested, what is being compared, which subject populations are involved in the research, and what is being measured. Operationally, these four factors refer to treatment design, research design, patient selection, and outcomes (102,104).

## Treatment Design

Treatment design involves the extent to which clarity about the “active ingredients” of the procedure being tested can be achieved. Questions to be answered include whether the procedure involves a single treatment, a combination of treat-

ments, or a combination of treatment and non-treatment factors. Often, because apheresis procedures involve a complex interplay of many factors (i.e., are “multivariant”), resulting research is confounded by inability to separate effects (85,117). The extent to which researchers can measure the impact of any one component of the procedure is limited when all patients receive or have access to multiple components concurrently. Clarity of design is essential to being able to attribute outcomes to particular treatments or packages of treatments.

Because it is an experimental therapy, the use of apheresis has not been standardized. Protocols in various studies have varied considerably. Variables include type of replacement fluid, patient selection criteria, other medications, extended respirator and intensive care therapy, and intensity of plasma exchange (i.e., frequency and volume exchanged in each treatment). Many different protocols have been used for apheresis, even in the treatment of a single disease, so that variation in procedures undoubtedly has led to variation in results (117). These variations make it difficult if not impossible to achieve some level of comparison between studies.

For example, apheresis is often used as an “adjuvant” or auxiliary therapy to immunosuppressive since drug therapy is required to inhibit the rebound reaction (see ch. 2). Although apheresis is used as an adjuvant therapy to anti-inflammatory, immunosuppressive, or cytotoxic drugs, this fact should not be viewed as a threat to its validity: any improvement in the course of disease would not be attributable to the pharmacological agents alone, but rather to the combined (or synergistic) effects of apheresis and drug therapy. There could be a validity problem, however, with the application of the treatment when the concomitant drug therapy varies across studies. When there is differential improvement by type of drug used, the integrity of the definition of treatment is called into question. Even though treatments are presented in the literature in a similar fashion, they may, in fact, operate quite differently. It may be the case that the combined (or synergistic) effects of apheresis and drug therapy may vary according to the strength of the drug and the frequency with which it is administered (85).

Even if standardized protocols could be developed, however, it may be difficult or undesirable to administer them. This is particularly problematic if, for research purposes, assignment to one group or another is required. Use of sham treatment in control groups, for example, could very well cause this group of patients to suffer some of the side effects of apheresis, raising the ethical question of subjecting them to a potentially harmful technique. (See the next section, “Safety: A Review of the Evidence,” for a discussion of the safety and risk issues of apheresis.) Another obvious ethical concern is whether treatment can be denied patients in near-fatal, disease states in which apheresis has served as the treatment of last resort. A third issue is the difficulty of setting up a controlled trial for some rare autoimmune diseases such as Goodpasture’s syndrome, which strikes only 2 out of 100,000 people in the United States every year (22,34). Even with autoimmune diseases of more common occurrence, such as systemic lupus erythematosus, presentation of disease symptoms can occur with such broad variety that setting up controlled trials for these conditions can become equally difficult (49).

A last treatment design problem has to do with possible placebo effects of the therapy itself. For example, among the several explanations discussed in the literature for improvement of patients undergoing apheresis was the possible psychotherapeutic effects of such therapy. Few studies have involved double blind protocols (with sham apheresis) which are necessary to eliminate the possibility of “placebo improvements” (85, 117,138).

## Research Design

A valid research design, perhaps most importantly, requires systematic comparison. At minimum, these comparisons involve the same group of patients measured before and after treatment; optimally, they involve two or more randomly assigned groups tested before and after treatment (147). The latter design is usually called a true experiment (25,122) or, in health care research, a randomized clinical trial (RCT). The advantage of this design, in comparison to nonrandom selection design, is that differences in outcomes can

be attributed more confidently to the treatment, rather than preexisting differences in the sample populations tested (102,104).

Evaluating existing research on apheresis therapy poses difficulties in any attempt to draw valid conclusions. Other than references to prior treatment regimens, comparative data on treatment groups are typically not available. The great majority of the reported studies are case reports without any concurrent control groups, blinding, randomization, or other techniques used in controlled clinical trials.

Because of operational and ethical difficulties discussed with treatment design issues (see last section), even well-controlled trials of apheresis have often suffered from small sample sizes. A small sample size for RCTS, for example, can undermine what would otherwise be considered a strong methodological study (85).

Related to the issue of appropriate research design is that multivariate analyses (useful for examining differences by such factors as age, sex, disease state, and levels of disability) are largely unavailable. Studies which statistically control outcome data have not been conducted because such analyses require large patient populations and present difficulties both in data collection and analysis. Their absence from the literature, along with the lack of controlled research, hinders informed development of treatment strategies tailored to subpopulation needs (102,104).

**Apheresis researchers**, however, seek to generate systematic experimental designs with comparison group information and multiple, longitudinal outcome measures. This is reflected by the increasing number of well-controlled studies both recently reported and presently being carried-out (see “Conclusions and Directions for Future Research” section of this chapter).

## Patient Selection

Patient selection refers to decisions concerning eligibility for treatment, selection for participation in research, and availability for follow-up research. If the general population of apheresed patients is not represented in the research samples because of particular characteristics (e.g., poorer

prognosis, differing remittive drug regimens), the generalizability of the research findings is limited and selection bias is bound to occur (102,104).

Perhaps the most severe sampling problem in apheresis studies stems from the use of the therapy as a last resort, i.e., for the “worst cases.” Typically, apheresis therapy has been initiated when patients diagnosed with a specific disease do not respond to other conventional therapies, including drug therapies and other forms of dialysis such as hemodialysis or peritoneal dialysis. The application of apheresis in the most severe cases of rheumatoid arthritis with multiple complications, for example, has been reported to correspond to what Warner (141) has labeled the “desperation reaction,” where patients and their physicians are highly motivated to try any promising therapy because continued painful symptoms or death is the likely outcome without the therapy and there is no effective alternative treatment available. High motivation can likely play an important role in the patient’s response to a number of subjectively determined outcome criteria, producing overly optimistic results (85). At the same time, if only the “worst cases” are selected for apheresis, its potential effectiveness may be underestimated because of its initiation at too late a stage in the disease process.

There is further the problem of statistical regression. According to Wortman and Saxe (147) “statistical regression arises when patients are chosen because of their extreme value on a laboratory test or other measure relevant to treatments.” Investigators have found that subjects with high pre-treatment measures tend to have lower scores after the treatment-when, in fact, no change has taken place. This is the statistical regression effect and it can deceive clinicians into believing that apheresis has been effective when it really has not (85).

## Outcome Measures

A recurring critical issue in any attempt to analyze the effectiveness of a medical technology is the selection of **appropriate endpoints for evaluating the success or failure of the intervention. The way in which outcomes of apheresis therapies are measured significantly affects interpretation of apheresis therapy research.**

Measures of assessment of outcome have varied enormously, both across and within disease indication categories. Appropriate outcome measures have at times focused on clinical improvement (i.e., improvement in signs and symptoms) often with reports of dramatic change. Clinical improvement measures, as defined in some apheresis studies, however, have been relatively “soft” or subjective endpoints where researchers fail to establish standards for any of the criteria, but rather look for general improvement across series of measures (85). In other instances, outcome measures are lacking, not specified, or ill-defined in the written reports.

Even when clinical outcome measures are well defined, it is important that the appropriate measure is used. When an outcome measure such as mortality is used to evaluate the effectiveness of apheresis therapy for hemolytic-uremic syndrome (characterized by a decay of general kidney function), for example, the benefits of apheresis may be substantially understated. Plasma exchange may, for instance, bring about a temporary improvement in the patient’s clinical status, but other intervening factors may ultimately cause the patient’s death. Most clinicians, however, would probably agree that the ultimate objective of apheresis therapy is to increase the likelihood of survival, which suggests that survival (or mortality) is an important outcome measure of the efficacy of apheresis and should not be disregarded. The need for chronic dialysis, on the other hand, could be a more appropriate outcome measure for determining the ultimate success of plasma exchange in the treatment of hemolytic-uremic syndrome, since renal failure is a major element of the syndrome (146).

**Interpretation of clinical improvement for many diseases treated by apheresis is further confounded by the variability produced by a basic “remitting-exacerbating” nature of the illness. Specifically, rheumatoid arthritis, systemic lupus erythematosus, myasthenia gravis, and Guillain-Barré syndrome patients frequently experience abrupt and**

pronounced improvements or worsening of the illness, and such spontaneous change can easily be mistaken for therapeutic effect. This leads to greater variability in results in clinical studies and to difficulty in interpreting the results (115,117).

Outcome measures have also focused on hematologic and biochemical parameters, such as nerve conduction tests, and immunological changes. These measures have not necessarily demonstrated any correlation to clinical responses, though. Sometimes they have preceded or coincided with clinical changes, while for other disease indications, they have shown no association to a clinical response. In short, such outcome measures may be necessary but insufficient indicators of the efficacy of apheresis (146). Simon (127), for example, recently reported the case of a woman with pemphigus vulgaris (a sometimes fatal skin disease), where apheresis allowed the disappearance of both skin and tissue-fixed antibodies, but in which the patient continued to have manifestations of the disease and subsequently died.

Perhaps hematologic and biochemical parameters could be combined in some way as co-measures with clinical improvement outcomes. The problem of combining multiple evaluation criteria and assessing the significance of the results is a difficult one. For example, researchers may choose to assign different weights to each outcome measure which would lead to disagreement and perhaps a lack of consensus on the effectiveness of apheresis therapy for certain disease indications (146).

Finally, outcome measures probably suffer from the lack of systematic documentation of adverse effects. As a new technology is developed, used, and reported, researchers and practitioners may also champion the technology for a variety of personal and professional reasons (104). Apheresis therapy reporting may have been biased by the tendency to report the more successful uses of the new therapy (115).

## SAFETY: A REVIEW OF THE EVIDENCE

The paucity of well-controlled trials creates difficulties for an unreserved assessment that apheresis is a safe procedure. Doubts about short- and long-term safety have neither been confirmed nor dispelled. Plasmapheresis, in its use for plasma collection in blood banking, has been demonstrated as a relatively safe procedure. Apheresis in its other forms does appear to carry some degree of risk, however, and results in a number of complications, especially when applied repeatedly for therapeutic applications (42).

Observational studies have generally asserted the procedure to be relatively safe and well tolerated by most patients, especially when performed by experienced personnel. Close and continual monitoring of the patient (at least during initial treatments that establish individual tolerance levels), however, is usually recommended to ensure that any complications be treated immediately should they occur. Unlike hemodialysis, where patients receive their blood back almost unchanged, there is much more room for error and miscalculation, because of the newness of the replacement mixture (80).

Borberg (13) reported that in 205 plasma exchange procedures, 4 serious reactions (anaphylaxis, collapse) and 23 moderate reactions (chills, stiffness, low blood calcium, fever) occurred. He further stated that the incidence of side effects was significantly reduced as the apheresis staff gained experience with the procedure.

Wenz and Barland (144) conducted a 10-year historical survey on plasma exchange and reported it to be a relatively safe procedure when performed by experienced personnel. Among the risks reported were massive extracorporeal blood clotting and viral hepatitis. However, there have been no clinical problems with hemorrhagic tendencies despite decreases (30 percent) in platelet counts following plasma exchange. Coagulation parameters returned to normal levels within 4 to 24 hours following the exchange.

In another study of the safety issue, Sutton, et al. (130), reported that of 887 plasma exchange procedures performed over a 3-year period, minor complications (chills, hypotension) occurred in

less than 7 percent of the exchanges. Citrate (an anticoagulant) toxicity (paresthesia and nausea) occurred in 5 to 15 percent of the exchanges. Sutton, et al. (130), did not see an increased risk of infection in these patients despite low levels of the third component of complement and immunoglobulins following the exchanges and the concurrent use of immunosuppressive drugs. In addition only two episodes of minor bleeding were reported, a further argument that patients receiving this type of therapy may not be predisposed to bleeding (145).

Generally, the major risks associated with apheresis may be grouped according to:

- **Problems of technique.** —Manual apheresis may run a risk of infection and also presents the possibility of returning the wrong cells to the patient. Automated centrifuge machines may create problems with hemolysis, platelet loss, or air-emboli entering the patient's bloodstream.
- **Complications associated with fluid transfer.** —Improper control of fluid balance may result in hypertension or cardiac arrhythmias in patients undergoing plasma exchange. The infusion of large volumes of intravenous fluids at room temperature may lead to hypothermia or chill reactions.
- **Side effects with replacement fluids.** —Each of the major types of protein replacement carries particular risks. The use of fresh frozen plasma may introduce hepatitis. Immunological reactions, including chills, skin eruptions, wheezing, and stiffness may occur in patients who are allergic to certain antigens in transfused plasma. The use of plasma protein fraction or albumin may cause hypotensive reactions or may result in platelet loss (108).

Long-term effects of fluid replacement are also worrisome. Removing lymphocytes and large volumes of plasma repeatedly could decrease immunocompetence levels, increasing the probability of patients' susceptibility to pneumonia and the like. A related concern is the risk of removing the cells that carry long-term immunological memory-B-cell

lymphocytes. Apheresis could make patients susceptible to some childhood disease they had been immune to formerly. Such diseases are often more serious for adults than children (57,80).

- **Anticoagulant reactions.** —The use of large amounts of citrate may result in hypocalcemia (low blood calcium) which requires the addition of calcium to the replacement fluids. The use of heparin as an anticoagulant can result in significant platelet loss (thrombocytopenia) if the procedure is extended over long periods (108).
- **Immunosuppressive drug reactions.** —As already discussed in chapter 2, the apheresis procedure is often accompanied by an immunosuppressive drug treatment regimen. These drugs are not without complications,

either. Since they are relatively nonspecific, the immune system in general is suppressed, and consequently patients on these drugs are prone to infection. These potent drugs can also damage vital organs, sometimes resulting in life-threatening inflammation and fibrosis of lungs, heart, intestines, or kidneys (42).

While all the above situations can result in serious complications, particularly for severely ill patients, many of these problems appear to occur rarely and often can be overcome by prompt diagnosis and attention. There have been six known fatalities among the thousands of apheresis procedures reported performed during the last 10 years (108).

## EFFICACY AND EFFECTIVENESS: A REVIEW OF THE EVIDENCE

Ideally, for any procedure, criteria should exist for the selection of patients; the intensity, frequency, and duration of the procedure; the choice of replacement fluids; the immunological parameters to be followed; and the clinical evaluation of the effects of the procedure. However, after a decade of use no firm guidelines for apheresis have been established (144).

Despite the lack of well-controlled and generalizable research on the efficacy and effectiveness of apheresis, there is a vast literature that describes and analyzes treatment effects. Because it is highly anecdotal, discussion of the evidence has sometimes been confined to speculation and generalities. **Still, the amount of research has dramatically increased and its quality has improved in recent years.**

This section presents and analyzes the evidence from several reviews of available literature. The discussion includes the scientific and medical assessments conducted by the National Center for Health Care Technology (NCHCT or Center) for Medicare coverage and reimbursement policy, \*

● The National Center for Health Care Technology (now succeeded by the Office of Health Technology Assessment) in the Department of Health and Human Services has been authorized by law since

and a number of assessments undertaken by medical associations and specialty societies. This section further presents evidence from original assessments completed for this case study on three disease indications for which apheresis therapy has been used experimentally, with somewhat favorable and hopeful results.

Medical applications and effects of apheresis are usually classified according to medical discipline, such as neurology and hematology, or according to the type of abnormal blood component removal (i.e., protein, antibody, immune complex, or cell). This section will utilize the latter approach. Table 3 classifies various diseases by both categories. For protein, antibody, and immune-complex component removal, the apheresis modality generally employed is plasma exchange, with lymphapheresis and lymphoplasmapheresis used to a lesser extent.

1978 to advise on issues related to the evaluation of health care technologies for reimbursement purposes by the Health Care Financing Administration and other third-party payers. For a complete discussion concerning this process the reader is referred, for example, to references 103, 104,

Table 3.—Selected Diseases Treated With Apheresis

Medical discipline	Plasma exchange			Cytapheresis
	Protein related	Antibody related	Immune complex related	
Hematology	Waldenstrom's macroglobulinemia	Idiopathic thrombocytopenic purpura (ITP) Factor VIII antibody Rh disease	Thrombotic thrombocytopenic purpura (ITP) <sup>b</sup>	Sickle cell Polycythemia
Rheumatology		—	Rheumatoid arthritis (RA) <sup>a</sup> Systemic lupus erythematosus (SLE) Scleroderma Other	Rheumatoid arthritis
Neurology		Guillain-Barré syndrome (GBS) Myasthenia gravis (MG) Multiple sclerosis (MS) <sup>a</sup> Polymyositis		Multiple sclerosis
Oncology Nephrology	Multiple myeloma —	Transplant rejection Goodpasture's syndrome (GS)	Other cancers Progressive nephritis  Glomerulonephritis	Some leukemias
Other	Toxins Poisons Hypercholesterolemia Thyrotoxicosis Primary biliary cirrhosis Hypertriglyceridemia			

<sup>a</sup>Preferred apheresis therapy not yet decided; clinical studies have employed plasmapheresis, Plasma exchange, lymphapheresis, and/or lymphoplasmapheresis.  
<sup>b</sup>Discussed in this chapter Under "Antibody Related Diseases."

SOURCE: Adapted from L. F. Rothschild, Unterberg, Towbin, 1981.

## Protein-Related Diseases

As discussed in chapter 2, protein-related diseases involve either excessive levels of proteins in plasma or excessive levels of other substances which are "carried" in the blood by the plasma proteins.

### Hyperviscosity Syndrome

The earliest therapeutic use of plasmapheresis was in the management of hyperviscosity syndrome associated with paraproteinemias. This group of diseases is characterized by the production of enormous amounts of protein molecules known as immunoglobulins, which are endowed with known antibody activity. *Waldenstrom's macroglobulinemia* results in the overproduction of one type of immunoglobulin-IgM and an increase in plasma viscosity or thickening leading to ocular, neurological, and cardiovascular problems. *Multiple myeloma*, a malignant tumor of the bone marrow, involves excessive production of other types of immunoglobulins—IgG, IgA,

IgE, or IgD—and may result in various symptoms including hyperviscosity syndrome, excessive bleeding, and renal failure. *Cryoglobulinemia* is characterized by the presence of abnormal immunoglobulins which "precipitate" or form antibody-antigen complexes in temperatures below 37 C. Symptoms include neurologic abnormalities, purpura, and "skin ulcers" (108).

Clinical studies as early as 1960 have generally confirmed the effectiveness of massive plasma exchanges in treating the hyperviscosity syndrome. A major reason for these findings is that patients' symptoms have classically correlated with levels of viscosity and direct removal of substances. Observers have rarely been led astray, with symptoms normally following the lowering of the viscosity levels in these disease states (58,108,127).

In Waldenstrom's syndrome, there seems to be little dispute that apheresis is an effective palliative measure in the removal of excess protein. In severe cases, it probably represents the only effective

treatment modality (42,117). With multiple myeloma, apheresis has been demonstrated to be effective in the acute treatment of crises associated with this condition. Improvement is temporary, but it can permit chemotherapeutic attempts to bring the disease under control. In terminal patients who fail to respond to chemotherapy, apheresis is finding use as a palliative measure to manage hyperviscosity symptoms. The disease is ultimately fatal, but apheresis has improved and prolonged the quality of life for some patients (117). Several groups have reported definite responses from apheresis for treating the symptoms of cryoglobulinemia, but there are no known results of controlled studies for this indication (58,108).

In February 1981, NCHCT in response to a Medicare coverage issue request, recommended that, as a safe and effective therapy, apheresis be covered in the “treatment of primary macroglobulinemia (Waldenstrom) and hyperglobulinemias, including multiple myeloma. These indications would include hyperviscosity states and cryoglobulinemias associated with these conditions” (54). The American College of Physicians, through its Clinical Efficacy Assessment Project (for more information see, for example, 104), also seems ready to concur. In a draft statement (4) prepared for NCHCT, they call apheresis an “efficacious and standard therapy in the treatment of hyperviscosity syndromes such as those secondary to Waldenstrom’s macroglobulinemia and multiple myeloma.”

#### Hypercholesterolemia

Likewise, apheresis has been used to remove other direct substances in the plasma such as cholesterol. **Familial hypercholesterolemia** is a common, usually inherited disease characterized by increases in plasma cholesterol leading to nodules of cholesterol forming on the skin or within the nervous system and to premature closing of the arteries. The use of apheresis has been undertaken at several hemapheresis centers with varying results. There has also been some anecdotal evidence of cholesterol levels being lowered and resulting clinical improvements in patients suffering from disorders related to **primary biliary**

cirrhosis, characterized by enlargement of the liver and retention of bile (108).

#### Protein Bound Factors

Certain classes of hormones, toxins and poisons have also been found to be bound to plasma proteins, and this has provided the rationale for the use of apheresis in treating the life-threatening symptoms that often result from the presence of excessive concentrations of these substances. Again, the removal of these substances has often correlated with clinical success, but controlled studies have not been earned out. In most of these conditions, however, apheresis is utilized only as a short-term, emergency measure (108,127).

**Thyrotoxicosis** is a condition that results from excessive production of hormone by the thyroid gland. Removal of the substance by apheresis has been reported to alleviate crisis symptoms (a crisis stage is referred to as a **thyroid storm**).

**Hepatic coma** is thought to be due to the accumulation of protein bound toxins in the bloodstream as a result of acute liver failure arising from a number of causes such as acute viral hepatitis, cancer, or reaction to anesthesia. Plasma exchange, and more recently plasma perfusion, have been observed to be effective in reducing toxins until the liver has had a chance to regenerate itself. Plasma exchange regimes, though, remain highly variable for treatment of hepatic coma (108).

**Refsum's disease** is a chronic, hereditary disease characterized by ocular disorder, loss of sensory and motor function, and dry scaly skin. Equivocal responses in individual cases have been reported (80).

Lastly, apheresis has been used in the treatment of poisonings. The procedure has been thought to be particularly applicable to those toxins that are not removed by dialysis, such as mushroom-poisoning. Protocols have varied widely, according to setting and according to type and amount of poison (108,144).

#### Antibody-Related Diseases

As discussed in chapter 2, these diseases are often termed “autoimmune” diseases, in which

pathological antibodies are produced and, in turn, attack the body's own normal tissues. Researchers began to look to apheresis for treatment of this class of diseases because of the success in removing substances associated with hyperviscosity. It was hypothesized that by removing the antibodies which were thought to mediate the disease process, clinical results would correlate in a fashion similar to those found when immunoglobulins were removed for hyperviscosity symptoms (127). The two examples in this category with the most data are myasthenia gravis and Goodpasture's syndrome, both discussed in this section.

### Neurological Disorders

Apheresis has been applied in the treatment of several diseases of the nervous system. Apheresis research has been pushed on by the discovery that many of the neurologic diseases have immune components and perhaps may have an antibody associated with them that may be removed (127). Myasthenia gravis (MG) is characterized by severe muscular weakness (without atrophy) and progressive fatigue. The symptoms are generally thought to result from an autoimmune attack on acetylcholine receptors in muscles. Because apheresis removes the anti-acetylcholine receptor antibodies from plasma, it has been evaluated with approximately 125 patients at five major clinical centers over the past 4 years. Results have shown significant short-term improvements in selected MG patients in clinical studies. The therapy is generally becoming considered appropriate in severe cases as well as for patients who exhibit progressive myasthenia symptoms despite treatment with corticosteroids. It has also been favorably reviewed as being beneficial in the long term and among the most promising applications of plasma exchange in autoimmune disease (42,108,177,144). Additional presumptive evidence of effectiveness is the Health Care Financing Administration's (HCFA) reimbursement of apheresis for acquired MG since September 1981. While NCHCT never issued a formal assessment recommending coverage of this indication, it did specify in November 1980 that it had "no objection" to HCFA'S preparation of a national coverage instruction for apheresis in treating acquired MG (56).

Multiple *sclerosis* (MS) is a chronic neurological disease characterized by patches of hardened tissue in the brain or the spinal cord producing partial or complete paralysis, jerking muscle tremor, and a variety of other symptoms and signs. The cause of MS is unknown, but there is some evidence to indicate that the presence of increased amounts of immunoglobulins and antibodies in the nervous system may contribute to the disease. It has been suggested and reported that two types of apheresis procedures—plasma exchange and lymphapheresis—may be effective in controlling MS through removal of toxic blood factors (108,117).

Preliminary studies involving very small numbers of patients have reported significant improvement in the majority of "progressive MS" patients treated with plasma exchange. Several factors, however, make any conclusions from these studies tentative: 1) a plasma factor "specific" for the disease, such as an antibody, has yet to be identified; 2) the disease has a relapsing and remitting nature which makes conclusions from small samples extremely tenuous; and 3) immunosuppressive therapy, reported to be useful in MS by itself, accompanied plasma exchange in the studies (so that the effect of plasma exchange alone could not be determined) (117). An assessment of MS was conducted by NCHCT in response to a Medicare coverage issue, and reviewed both published and ongoing research. The Center concurred with the findings of the National Institute of Neurological and Communicative Diseases and Stroke (NIH) and the National Multiple Sclerosis Society that there is currently inadequate justification for the routine use of any form of apheresis in the management of MS. Although apheresis is still considered experimental, however, the Center noted several controlled clinical trials about to begin or underway that should help clarify the appropriate role for apheresis in the treatment of MS (91).

*Guillain-Barré syndrome* (GBS) is a viral inflammatory disorder of the brain, characterized by a great increase in the protein in the cerebrospinal fluid and in accompanying loss of sensory and motor function. The condition may be acute or chronic, and is sometimes fatal. Several cases of GBS have been associated with swine flu vaccinations (108,117).

A primary review, including a methodological assessment, of the apheresis literature in the treatment of GBS was prepared as part of this study. Case reports and small-scale, mostly uncontrolled trials provide suggestive evidence that apheresis may be effective for some patients with GBS. Because of the low mortality and good prognosis for most patients with GBS, however, the safety of the procedure and indications for its use need to be delineated prior to nonexperimental use of plasma exchange in GBS.

The conditions for use of plasma exchange in acute GBS have been sufficiently standardized to enable a controlled clinical trial of the procedure. The potential cost saving and potential for shortened disability make well-designed controlled studies of this therapy important. Controlled studies currently in progress should be adequate to provide data which address the essential clinical questions. Until the results of these studies are available, though, the use of plasma exchange in GBS can only be considered an experimental procedure (115). The full review and assessment of apheresis for the treatment of GBS is presented in appendix D.

Another neurological disorder for which apheresis has been reported (108) as a treatment approach is **amyotrophic lateral sclerosis** (ALS), a progressive disease marked by muscular weakness and atrophy. Norris, et al. (89), noted some improvement in three of ten ALS patients who underwent plasma exchange sessions. This has not been confirmed by other studies, however, and no rationale yet exists as to why it should be effective (43).

Lastly, two neuromuscular disorders, polymyositis and **dermatomyositis**, have been reported (108) as responsive clinically to apheresis therapy. Both disorders, characterized by progressive muscular inflammation and weakness, have been linked to antimuscle antibodies. The evidence in both disorders, however, is anecdotal. The American College of Physicians (4) has called apheresis an “investigational therapy” in the treatment of patients with polymyositis, but has also stated that it “maybe indicated . . . in patients in the severe, imminently fatal polymyositis . . . who are resistant to all other therapies.”

## Renal Diseases

**Goodpasture's syndrome (GS)** is characterized by a combination of glomerulonephritis (kidney disease) and pulmonary hemorrhage. The incidence of GS is approximately 4,000 to 5,000 cases annually in the United States. GS is believed to be caused by an antibody directed against glomerular (kidney) and alveolar (lung) basement membranes and is characterized by a rapidly failing course terminating in asphyxia from lung hemorrhage or in death from renal failure. Historically, the treatment of GS has involved immunosuppressive/anti-inflammatory drugs with only modest success. The mortality rate for this disorder has typically run about 75 percent (22,108).

It is possible that apheresis removes enough circulating antibodies to alter the course of the disease, but reports are mixed. Again, there have been no controlled trials, but case studies and literature reviews claim that apheresis has been effective for those patients with mild to moderate renal dysfunction, but who are suffering acute pulmonary complications or who are experiencing rapidly progressive kidney deterioration (4,108,117,144). It has been speculated that early diagnosis and apheresis therapy could prevent irreversible renal failure (42).

The American Medical Association has also supported apheresis in use of treatment of GS though it has not specified under what conditions (s). The American College of Physicians, however, has called apheresis an “investigational” therapy for GS, stating that studies to date have failed to demonstrate improved survival among patients with this disease receiving apheresis (4). A more thorough review and assessment of the use of apheresis for GS was completed in early 1983 by the Office of Health Technology Assessment (OHTA) in response to a Medicare coverage policy issue. The OHTA assessment reported the beneficial effects of plasma exchange for some groups of GS patients. However, probably because of the absence of prospective RCTs, OHTA recommended plasma exchange only be considered standard therapy for “life threatening forms” of GS (94).

In a related area of renal disorders, rejection of the donor kidney remains the major problem in renal transplantation. Acting on the hypothesis that rejection is due in part to a circulating antibody directed against the vascular endothelium, several groups have used intensive plasma exchange to treat renal *allograft rejection*. Scoville Associates (108) has reported that apheresis is apparently effective in controlling approximately 50 percent of acute rejection episodes, and that the graft survival period has been lengthened when apheresis is used in a combination therapy regimen with steroids versus use of steroid therapy alone. The role of apheresis in the management of acute renal transplant rejection (particularly in those cases which do not respond to steroid therapy) has been called promising, though, more well-controlled studies need to be undertaken at this point (30).

#### Blood Disorders

Another disorder for which *use* of apheresis has generated some initial response and promise has been in treatment of patients with *antibodies to Factor VII*. Apheresis has been investigated as a potential therapy for patients with antibodies or inhibitors to Factor VIII during the past 10 years. Factor VIII is a substance in the blood involved in hemostasis (i.e., the normal process of blood clotting for control of bleeding). Patients with the most common type of hemophilia lack Factor VIII and are at risk of developing Factor VIII antibodies when given supplemental, exogenous Factor VIII to help control bleeding episodes. It has been estimated that as many as 20 percent of such patients may develop this condition. Factor VIII inhibitors can also arise spontaneously in other patients. This so-called idiopathic or acquired inhibitor to Factor VIII can occur in women in their first year after giving birth, persons with rheumatoid arthritis, the elderly, and persons suffering a variety of other disorders (57,146).

As part of this case study, a primary literature review, analysis, and evaluation were undertaken for treatment of this disorder with apheresis. Nine studies were reviewed and both immediate and long-term findings were tallied. For 16 of the 18 patients at risk due to severe bleeding from surgery, the immediate clinical results were uniformly

successful. In all cases hemostasis was achieved, and the patient fully recovered from the acute episode. Nine patients were reported to have poor long-term results, but several patients were reported to have achieved a permanent reduction in Factor VIII inhibitor antibodies without the need for additional therapy. Importantly, though, the overall quality of the research evidence was found to be poor: the studies were all pretrial clinical reports (generally of one patient), there was no agreed upon treatment, the goals of the studies differed, and, with so few patients, the issue of sample bias should not be discounted (146). The complete assessment of apheresis in the treatment of antibodies to Factor VIII is presented in appendix C.

Antibodies to Factor VIII are encountered in a number of hematological (and nonhematological) disorders. Likewise, a host of hematological disorders are thought to be related to a gone-awry immune mechanism, and as a result, several blood disorders have been treated with apheresis, including thrombotic thrombocytopenic purpura, hemolytic-uremic syndrome, idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia, and rhesus hemolytic disease.

*Thrombotic thrombocytopenic purpura* (TTP) is an interesting example of a disorder for which apheresis appears to be of benefit as a lifesaving measure although the rationale for its use is still very speculative. It is a condition involving the development of diffuse, small blood clots and a deficiency of platelets. Its cause is unknown but may be related to a disordered immune mechanism acting directly on the platelets or on the blood vessels, or on both concurrently. Apheresis has been reported to have benefits in several cases, possibly by removing circulating immune complexes or an antiplatelet antibody. \* Results of apheresis for TTP have been encouraging with up to 80 percent response rates reported in some studies. The American College of Physicians' assessment (4) is typical of several reviews and of the research community (7,42,108,117,125,127, 144) in stating that "apheresis in conjunction with

\*Because of TTP's possible relation to immune complexes, this disorder is sometimes grouped under the immune-complex related disease category, and could logically be included in the next section's discussion ("Immune-Complex Related Diseases") as well.

exchange transfusions, corticosteroids and platelet inhibitors, appears to be efficacious and standard in the treatment of thrombotic thrombocytopenic purpura." The American College of Physicians noted further that, "Despite the fact that trials indicating efficacy were uncontrolled, the reductions in mortality in patients with TTP compared to those not receiving apheresis were so significant that apheresis appears to be beneficial." Simon (128) has also claimed that selective use of apheresis can also decrease morbidity, hospital stays, long-term chronic dialysis, and maintain a productive lifestyle for patients longer. NCHCT (92) conducted an assessment of TTP for Medicare coverage policy, and noted the reported beneficial effects, but cautioned that the quality of research was plagued by the complete absence of controlled clinical trials to confirm these findings. (Some have argued that such trials are impossible given the sudden and life-threatening intensity of the disorder's onset.) NCHCT, because of the life-threatening nature of TTP, stated that the use of apheresis (specifically, plasmapheresis and plasma exchange) "seems justified when other conventional therapies have failed."

Hemolytic-uremic syndrome (HUS) is characterized by a decay of kidney function, destruction of red cells, and a dramatically reduced level of circulating platelets. It shares a number of features with TTP. In fact, HUS has been considered by some clinicians to be a variant of TTP, this being supported by overlapping clinical and pathologic characteristics and the possibility of similar precipitating events. There is no objective method at present to distinguish HUS from TTP, although in the case of the former, the kidney is typically the main and often only target organ, children are primarily affected, and the prognosis is generally much better (71,146).

A primary literature review and assessment was conducted by Wortman and Murt (85) for this case study on the use of apheresis in the treatment of HUS. Data from the eight communications that have appeared in the literature during the past 3 years are presented on a total of 11 patients, but each case is described individually. Only one of the communications suggests that plasma exchange has limited effectiveness on the disease process (11). However, the authors in this article

add that the clinical benefit may have been compromised because apheresis was performed during a recurrent phase of the illness (which is recognized as being associated with poor prognosis). The remaining seven studies are almost uniformly favorable in suggesting that apheresis contributes to clinical improvement although there is no explanation provided about which measures are used to gauge this improvement. Several authors add the caveat that apheresis be initiated during the early stages of the disease in order to realize its full benefit (132). Parries, et al. (106), caution that apheresis alone is associated with complications (e.g., hepatitis) and that these risks should be weighed against the potential benefits of apheresis.

As might be expected with a total reporting of 11 patients, the research base is too small and incomplete to endorse apheresis as a treatment for HUS. Furthermore, the studies contain no comparison groups, while treatment designs and outcome measures varied widely, further limiting the ability to make any conclusion or recommendation. A full discussion of this assessment is found in appendix B.

**Rhesus hemolytic disease (Rh disease)** of the newborn is characterized by fetal anemia, jaundice, enlargement of the liver and spleen and general edema. Approximately 65 percent of untreated cases result in stillbirth or infant mortality. The disease is caused by Rh antibodies produced in maternal blood which may cross the placenta and destroy fetal red blood cells. Antibodies, directed against an Rh positive fetus, develop in an Rh negative mother following a previous pregnancy in which the fetus was Rh positive or following transfusion of Rh positive blood (108).

Murt (85) has reported that between 1968 and 1981, 13 studies were published on the effects of apheresis in the management of severe Rh disease. The quality of the research studies is quite poor: all 13 studies are observational, and all but one are reports of individual case studies. The number of patients in these studies ranges from 1 to 96 and the median is 3. Only 3 of the 13 studies have given plasma exchange an unfavorable review, and 2 of these studies are the initial published reports of the use of apheresis in treating pregnant women with Rh disease (14,112).

There are a host of other autoimmune hematological disorders treated by apheresis. Such disorders include autoimmune hemolytic *anemia* and *idiopathic thrombocytopenic purpura*. They are caused by antibodies which characteristically attack and lead to the destruction of valuable blood components. These diseases have been treated with some success with apheresis, but the reports are anecdotal (42).

### Immune-Complex Related Diseases

In immune-complex related diseases, antigen-antibody complexes can be deposited in tissue and produce severe inflammation and tissue damage. Just as researchers and clinicians reasoned that protein plasma substance removal could be extended to antibody removal, circulating immune complexes began to be experimentally removed through apheresis methods.

#### Renal Disorders

This further extension to immune complexes was particularly notable in England and Australia where there was an initial interest by nephrologists in the application of apheresis for rapidly progressive *glomerulonephritis (GN)* (127). Characterized by a rapid deterioration of renal function, GN appears to arise from two mechanisms. The first mechanism stems from the deposition of immune complexes which are formed in the circulation and subsequently lodge in the glomeruli (small structures in the kidney which contain capillary blood vessels surrounded by a thin membrane which acts as a filter for the separation of urine). The second mechanism, the much rarer, arises when an antibody is generated against the kidney, which sets in process a chain of inflammatory events leading to GN. Plasma exchange for rapidly progressive GN has been evaluated as a therapy mode with rather uncertain results (90,108). Several case studies have been published reporting the clinical success of patients treated with concurrent plasma exchange and immunosuppressive drug therapy. However, there is some speculation that similar results may be obtainable with immunosuppressive drug therapy alone (108, 128). Apheresis in rapidly progressive GN has also been associated with a high degree of infection caused by a variety of unusual pathogens (42).

NCHCT was requested by HCFA in May 1981 to conduct an assessment of the safety and clinical effectiveness of “membranous and proliferative glomerulonephritides” for Medicare coverage and reimbursement policy (38). Due to budgetary and staff cutbacks, that assessment was not issued until early 1983 by NCHCT’s successor organization, the Office of Health Technology Assessment (28). The OHTA assessment concluded that for rarer types of GN (antibody related), it appeared that plasma exchange “favorably affected” GN, and “should be recommended as standard therapy” for these conditions. However, for those more common cases of GN associated with immune complex mechanisms, OHTA concluded that the role of apheresis is “much less clear-cut and should be investigated further” (94).

#### Connective Tissue Disorders

The advocated clinical successes in GN led to investigative and experimental usage of apheresis in a whole host of connective tissue diseases which were thought to be possibly related to immune complex deposition in tissues and often correlated with levels of circulating immune complexes (127).

*Systemic lupus erythematosus (SLE)* is a chronic and often fatal disease characterized by pathological changes in the vascular system, manifested in skin rashes, fever, arthritis, and heart, lung, and kidney damage (108). Preliminary reviews indicate that apheresis has produced “striking short term clinical improvement” in some patients with high levels of circulating immune complexes before treatment. However, other patients with SLE, but not high levels of circulating immune complexes before treatment, have also responded to therapy. Study results have also been confounded by poorly controlled immunosuppressive and anti-inflammatory drug therapy accompanying apheresis (117, 128). As with apheresis in the treatment of rapidly progressive GN, HCFA requested NCHCT in May 1981 to assess the safety and clinical effectiveness of apheresis therapy for SLE as a candidate technology for Medicare coverage and reimbursement. That assessment, now under the aegis of OHTA, has not yet been completed (28). The American College of Physicians (4) and the American Society of Hematology (7) have both judged apheresis for SLE as “in-

vestigational” only, noting that no adequately controlled scientific studies have established its efficacy. Both groups, however, cautiously allow for the possibility of use in critically ill SLE patients who fail to respond to conventional drug therapy.

**Rheumatoid arthritis (RA)** is a chronic disease of the joints marked by inflammation and atrophy of the bones. In late stages, deformity and immobility develop. While it is unclear at present which plasma factors are involved in RA (immunoglobulins, immune complexes, lymphokines, etc.), several medical centers have reported beneficial effects of plasma exchange or related procedures: lymphapheresis and lymphoplasmaapheresis. Several apheresis protocols have been reported. Clinical responses have been claimed in the remission of symptoms that lasts several months (117). Rothwell, et al. (118), however, reported no statistically different clinical response in a controlled study that had one group receive plasma exchange and drug therapy while a second group received drug therapy only.

Because RA affects approximately 7 million individuals in the United States, with no known cure, the question of apheresis treatment benefits has become a somewhat volatile issue. Over the past 2 years, the Council on Scientific Affairs of the American Medical Association, the American Rheumatism Association, the American College of Physicians (who consulted with the American Society of Hematology and the American Society of Oncology, as well), and NCHCT have all formally considered the evidence. All have concurred that apheresis for treatment of RA is an experimental therapy but have suggested its possible use in serious, life-threatening complications of RA, such as vasculitis, cryoglobulinemia, or hyperviscosity syndrome (59,86). In a separate assessment, NCHCT explicitly recommended apheresis in the management of life-threatening **rheumatoid vasculitis\*** as a treatment of last resort and possibly lifesaving intervention when more conventional therapies have failed. The Center stated that such “pro-

cedures are usually reserved for those patients who have failed to respond to more conventional therapies and it is usually combined with them” (93).

There is also some current debate about the proper mix of apheresis therapy and drug therapy for RA and about the relative effects of plasma exchange and lymphocyte removal. Studies are still needed to define the role of each therapy in the management of severe RA. Wallace, et al. (139), have recently reported the results of a double-blind, controlled study of lymphoplasmaapheresis versus sham apheresis in RA for 14 patients. The results proved mixed. Whereas some measures of disease severity improved significantly in the treated group as compared with the control group, others did not. All reported benefits of therapy were temporary (12).

**Cutaneous vasculitis**, an additional connective tissue disorder treated with therapeutic apheresis, is characterized by inflammation of the small blood vessels of the skin. Temporary clinical responses have been reported in the literature. There are no known controlled studies (108).

#### Skin Disorders

Several dermatologic diseases which are thought to involve immune mechanisms have indicated a response to therapeutic apheresis. **Pemphigus vulgaris** is a rare disorder characterized by bubblelike lesions on the surface of the skin. Remissions have been reported with apheresis, but there are no published clinical trials (2,108,144). Single cases of clinical responses to **herpes gestationis**, a subepidermal blistering condition of pregnancy, and **psoriasis**, a chronic, genetically determined dermatitis, have also been reported (108).

#### Cancers

Therapeutic apheresis in the treatment of multiple myeloma was discussed earlier in this chapter. Several reports have also described recent attempts to treat various forms of other cancers with plasma exchange. Animal studies have suggested that the growth of the tumors is related to deficiencies in the immune process (144). The rationale for apheresis is that the removal of immune

\*Rheumatoid vasculitis is marked by a destruction and necrosis of sections of the body, particularly toes and fingers and areas served by small vessels that are inflamed.

complexes or blocking factors might improve immune responsiveness to tumors. Preliminary results have been mixed and further evaluation will be required. A refinement of plasma exchange, involving modification of plasma (by circulating it through protein-A columns) has recently been reported to produce benefits in several forms of cancer, including breast cancer (117).

At the beginning of this century, hopes for developing vaccines for treatment and specific diagnostic tests for cancer were based on remarkable advances in immunology and their successful application to many infectious diseases. Early efforts to relate immunology and cancer failed because of a lack of understanding of the complexity of the immune response. In recent decades, however, investigations have discovered a probable role of the immune system in both the development and spread of tumor cells (108). **At present, apheresis for cancer is experimental, but it could broaden the fundamental understanding between malignancy and the immune response (144).**

#### Miscellaneous Disorders

Table 4 presents a list of diseases either believed to be of immunological origin or of unknown cause for which plasma exchange has been experimentally employed as a therapy and positive clinical responses reported. Typically, in each disease category, plasma exchange procedures have involved only a small sample group anywhere from 1 to 30 patients and there have been no control or comparison groups against which to measure treatment results. Evidence, then, is

**Table 4.—Therapeutic Apheresis for Miscellaneous immunological Diseases and Diseases of Unknown Cause**

<i>Miscellaneous immunological diseases</i>	
	Graves' disease
	Crohn's disease
	Severe asthma
	Insulin-resistant diabetes
	Scleroderma
Diseases of unknown cause	
	Hypertension (idiopathic only)
	Raynaud's phenomenon
	Idiopathic pulmonary hemosiderosis

SOURCE: Adapted from Scoville Associates, 1981.

anecdotal and awaits additional research before reliable conclusions can be drawn regarding the potential role of apheresis for these disorders (42,80,108,144).

#### Cell-Related Diseases

The use of apheresis (specifically cytopheresis) therapy has been anecdotally reported to be quite beneficial in the treatment of diseases involving excess or abnormal blood cellular components. While not common, certain clinical situations may benefit from the removal and lowering of a platelet count or white blood cell count in a patient. Very high white counts, such as in **granulocytic leukemia**, can cause immediate and severe crises with cerebral hemorrhaging, and possibly death. Emergency removal of white cells can be lifesaving while chemotherapy is initiated, although chronic treatment has generally failed to alter the outcome of the diseases. **Sickle cell disease** (SCD) is characterized by red blood cells (RBCs) containing abnormal hemoglobin. The "sickling" of RBCs in capillaries impairs blood flow and can produce severe complications. Exchange transfusion (removal of RBCs followed by replacement with normal RBCs) has been reported to produce beneficial results in SCD crises. Also, long-term use of platelet removal and white cell removal in the treatment of autoimmune diseases, including multiple sclerosis and rheumatoid arthritis, have also been reported, and research in those areas continues.

Although not for therapeutic purposes, cytopheresis applied to healthy donors also has important clinical applications in the preparation of component concentrates. Many diseases involve decreased levels of white cells or platelets. Cancer chemotherapy, as well, often depresses bone marrow production of white cells and platelets so that transfusions of the deficient components are clinically beneficial. Recent refinements in blood separator devices make it practical to collect large numbers of platelets or white cells from a single donor rather than pooling separate components from multiple donors. This is of considerable benefit in minimizing the risk of donor/recipient antigenic incompatibility and hepatitis transmission (117).

## CONCLUSIONS AND DIRECTIONS FOR RESEARCH

Clearly, a variety of diseases—often rare—have been treated by apheresis in circumstances where conventional therapy has not been beneficial. There is a great deal of enthusiasm among researchers and clinicians who wish to explore all the possibilities for therapeutic apheresis. Medical journals are replete with anecdotal reports of physicians' trying apheresis as a last resort in a wide range of diseases. These cases, however, do not provide a strong systematic base for recommending the widespread use of apheresis as a mature and effective technology.

Apheresis appears to be a relatively safe procedure, though it is not without at least short-term risks. The long-term risks of removing useful blood components have been termed "worrisome" and are unclear at best (80). Apheresis device equipment can also be termed effective in the sense that the technology accomplishes the intended removal of plasma and cells.

However, there have been very few well-controlled studies documenting the efficacy of the technology in actually improving health (53). More specifically, there have been few situations in which isolated pathogenic proteins, antibodies, immune complexes, and blood cells were removed and unequivocal clinical results observed. The use of apheresis has been generally acknowledged as an effective treatment application for acute therapy in a small group of relatively obscure diseases. These include acquired myasthenia gravis, primary macroglobulinemia (Waldenström's), and hyperglobulinemias, including multiple myeloma. There is certainly suggestive evidence, too, that therapeutic apheresis is successful in arresting the disease process for some patients under some disease conditions. Convincing proof of clinical efficacy, however, is still lacking in the wider variety of diseases in which this treatment is being used.

Any interpretation of clinical results has been further hampered by the lack of standardized application of this therapy. Criteria for patient selection and treatment schedules for many disease applications still need to be developed. The relative roles of exchange, drugs, and supportive care need to be further defined and clarified.

The problem of standardized application of apheresis is not surprising in considering that the scientific rationale for use of the technology to treat a specific disease category is sometimes very weak. Because the disease-causing mechanisms remain largely unknown, speculation has necessarily determined the intensity of the apheresis schedule, the volume exchanged, and whether there should be concomitant removal of cellular components with or without the addition of immunosuppressive drugs. Each of these aspects of apheresis has been the subject of much discussion and disagreement (12).

Though some researchers say it is "too early" to do controlled trials because doctors have not yet determined the theoretically best treatments to be tested, research in apheresis seems to be in transition. In an effort to document the value of therapeutic apheresis, large prospective randomized trials have been organized for several disease applications in which apheresis therapy has not been shown to be either clearly effective or ineffective (2,12). Although some of this research is being done without direct government support, a substantial portion of experimental and clinical trial work is being undertaken with the help of the National Institutes of Health (NIH). Because of the high costs of these studies, it is not surprising—or unreasonable—that public moneys support such a significant number of them. Table 5 presents a listing of major ongoing research studies.

In order to precisely define what advantages, if any, apheresis would have, controlled trials need to address the safety and efficacy issues discussed in this chapter of present apheresis technologies. Long-term studies will also be needed to detect any additional unforeseen or unspecified questions of safety, as well as effectiveness. Importantly, future research must also compare the present treatment modalities with new and emerging approaches such as plasma filtration through specific affinity columns (with the return of the patient's own plasma) or related scientific advances such as the use of monoclonal antibodies (see "Future Technological Directions" section in ch. 2 for a discussion of these treatment approaches). Many researchers and observers in

both the public and private sectors speculate that therapeutic apheresis as now applied will be replaced over the next 10 years by either advances in equipment-embodied apheresis technology or basic scientific research into the causes of various

diseases (53). If the present applications of therapeutic apheresis are indeed in such a period of flux, great care must be taken to target research and clinical efforts into the most promising and beneficial technology-related developments.

Table 5.—Present Apheresis Research Activity

Location	Principal investigator	Disease indication
<i>Major NIH Stud/as</i>		
SUNY—Stony Brook . . . . .	Gorevic, Peter	Cryoglobulinemia
Washington University . . . . .	Shonfeld, G.	Familial hypercholesterolemia
Cincinnati General Hospital . . . . .	Stein, Evan	Familial hypercholesterolemia
Johns Hopkins University . . . . .	Kwiterovich, Peter	Hypercholesterolemia, xanthomatosis, atherosclerosis
NIADDK, NIH . . . . .	Balow, J. E.	Goodpasture's syndrome
Walter Reed Army Medical Center . . . . .	Johnson, John	Goodpasture's syndrome and rapidly progressive glomerulonephritis
University of Cincinnati . . . . .	Pollak, Victor	Glomerulonephritis
Massachusetts General . . . . .	Coggins, Cecil	Glomerulonephritis
NIADDK, NIH . . . . .	Klippel, J. H.	Systemic lupus erythematosus
Rush-Presbyterian St. Lukes . . . . .	Lewis, Edmund	Systemic lupus erythematosus
Cincinnati General Hospital . . . . .	Kashvap, Moti	Systemic lupus erythematosus
Rush-Presbyterian St. Lukes . . . . .	Lewis, Edmund	Lupus nephritis
George Washington University . . . . .	Lachin, John	Lupus nephritis
University of Iowa . . . . .	Hunsicker, Lawrence	Lupus nephritis
University of Pennsylvania . . . . .	Schumacher, H.	Rheumatoid arthritis
NIADDK, NIH . . . . .	Wilder, R. L.	Rheumatoid arthritis
Scripps Clinic and Research Foundation . . . . .	Vaughan, John	Rheumatoid arthritis
Columbia University . . . . .	Jacobs, Jerry	Rheumatoid arthritis
Mayo Foundation . . . . .	Bunch, Thomas W.	Rheumatoid arthritis
SUNY at Brooklyn . . . . .	Diamond, Herbert S.	Rheumatoid arthritis
Columbia University . . . . .	Chess, Leonard	Rheumatic disease
Boston Children's Hospital . . . . .	Weiner, Howard	Multiple sclerosis
University of Utah Medical Center . . . . .	Petajan, Jack	Multiple sclerosis
Peter Bent Brigham Hospital . . . . .	Weiner, Howard	Multiple sclerosis
Johns Hopkins Hospital . . . . .	McKhann, Guy	Guillain-Barré syndrome
Miami Veterans Medical Center . . . . .	Lian, Eric	Thrombotic thrombocytopenic purpura
University of Rochester . . . . .	Marder, Victor	Idiopathic thrombocytopenic purpura
Cincinnati General Hospital . . . . .	Glueck, Charles	Lipoprotein metabolism
Columbia University . . . . .	Edelson, Richard	Pemphigus
Johns Hopkins University . . . . .	Moser, Hugo	Refsum's disease
NCI, NIH . . . . .	Stevenson, H. C.	Cancer
NCI, NIH . . . . .	Schiffer, C. A.	Leukemia
University of Texas . . . . .	Tindall, Richard	Neuromuscular disorder
University of New Mexico, Albuquerque . . . . .	Simon, Toby	Neonatal adaptation
Columbia University . . . . .	Grossman, Marc	Porphyria cutanea tarda
Columbia University . . . . .	Jaffe, Israeli	Connective tissue disorder
Columbia University . . . . .	Resor, Stanley	Dermatomyositis, polymyositis, and polyneuropathy
Tufts University . . . . .	Agnello, Vincent	Immune complex disease
Johns Hopkins University . . . . .	Moser, Hugo	Hunter's syndrome
<i>Other major studies</i>		
Rogovin Kidney Center . . . . .	Saal, Stuart	Myasthenia gravis
Evanston Hospital (Ill.) . . . . .	Dau, Peter	Myasthenia gravis, multiple sclerosis
Southwestern Medical School . . . . .	Tindall, Richard	Myasthenia gravis
El Dorado Hospital . . . . .	Giordano, Gerald	Multiple sclerosis
Froedtert Memorial Lutheran Hospital . . . . .	Khatri, Bhupendra	Multiple sclerosis
Kingston General Hospital, Ontario . . . . .	Giles, Alan	Rheumatoid arthritis
Toronto Western Hospital . . . . .	Cardella, Carl	Renal transplant rejection
Froedtert Memorial Lutheran Hospital . . . . .	Kaufman, H. Myron	Renal transplant rejection
Victoria Hospital, Ontario . . . . .	Clark, William	Lupus nephritis
Hammersmith Hospital, London . . . . .	Lockwood, Martin	Rapidly progressing glomerulonephritis
Canadian Red Cross (sponsor) . . . . .	Rock, Gail	TTP, ITP, Rhesus Iso-immunization

SOURCE: National Institutes of Health, 1982