The Safety, Efficacy, and Cost Effectiveness of Therapeutic Apheresis

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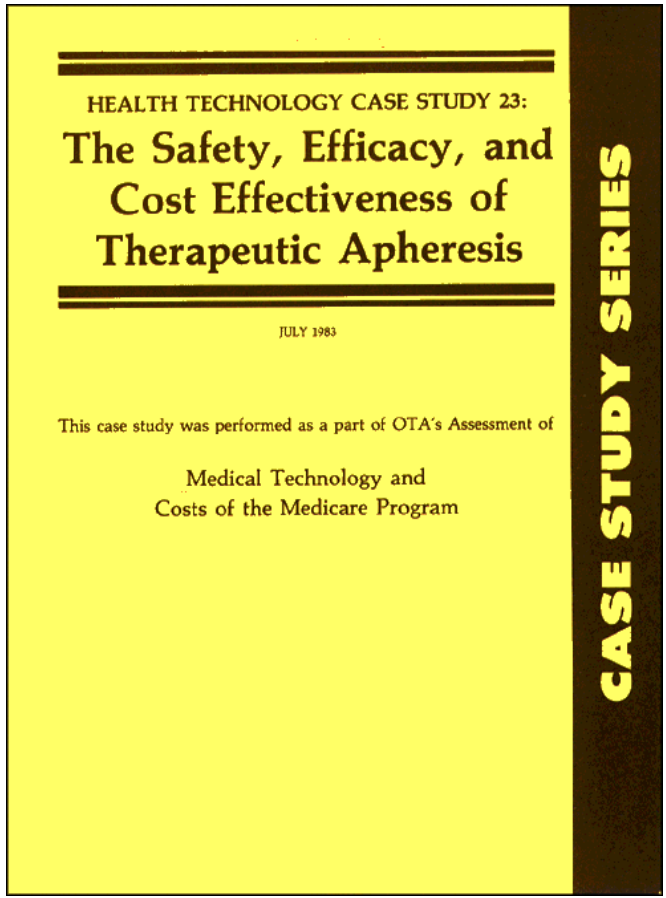

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Preface

The Safety, Efficacy, and Cost Effectiveness of Therapeutic Apheresis is Case Study **#23 in** OTA's **Health** Technology Case Study Series. It was prepared in response to a request by the Senate Finance Committee, Subcommittee on Health, and is part of OTA's project on ***Medical Technology and Costs of the Medicare Program,*** requested by the House Committee on Energy and Commerce and its Subcommittee on Health and the Environment. A listing of other case studies in the series is included at the end of this preface.

OTA case studies are designed to fulfill two functions. The primary purpose is to provide OTA with specific information that can be used in forming general conclusions regarding broader policy issues. The first 19 cases in the Health Technology Case Study Series, for example, were conducted in conjunction with OTA's overall project on ***The Implications of Cost-Effectiveness Analysis of Medical Technology.*** By examining the 19 cases as a group and looking for common problems or strengths in the techniques of cost-effectiveness or cost-benefit analysis, OTA was able to better analyze the potential contribution that those techniques might make to the management of medical technology and health care costs and quality.

The second function of the case studies is to provide useful information on the specific technologies covered. The design and the funding levels of most of the case studies are such that they should be read primarily in the context of the associated overall OTA projects. Nevertheless, in many instances, the case studies do represent extensive reviews of the literature on the efficacy, safety, and costs of the specific technologies and **as** such can stand on their own as a useful contribution to the field.

Case studies are prepared in some instances because they have been specifically requested by congressional committees and in others because they have been selected through an extensive review process involving OTA **staff and consultations** with the congressional staffs, advisory panel to the associated overall project, the Health Program Advisory Committee, and other experts in various fields. Selection criteria were developed to ensure that case studies provide the following:

- examples of types of technologies by function (preventive, diagnostic, therapeutic, and rehabilitative);
- examples of types of technologies by physical nature (drugs, devices, and procedures);
- examples of technologies in different stages of development and diffusion (new, emerging, and established);
- examples from different areas of medicine (e.g., general medical practice, pediatrics, radiology, and surgery);
- examples addressing medical problems that are important because of their high frequency or significant impacts (e.g., cost);
- examples of technologies with associated high costs either because of high volume (for low-cost technologies) or high individual costs;
- examples that could provide information material relating to the broader policy and methodological issues being examined in the particular overall project; and
- examples with sufficient scientific literature.

Case studies either are prepared by OTA staff, are commissioned by OTA and performed under contract by experts (generally in academia), or are written by OTA staff on the basis of contractors' papers.

OTA subjects each case study to an extensive review process. Initial drafts of cases are reviewed by OTA staff and by members of the advisory panel to the associated project. For commissioned cases, "comments are provided to authors, along with OTA's suggestions for revisions. Subsequent drafts are sent by OTA to numerous experts for review and comment. Each case is seen by at least **30,** and sometimes by 80 or more outside reviewers. These reviewers may be from relevant Government agencies, professional societies, consumer and public interest groups, medical practice, and academic medicine. Academicians such as economists, sociologists, decision analysts, biologists, and so forth, as appropriate, also review the cases.

Although cases are not statements of official OTA position, the review process is designed to satisfy OTA of each case study's scientific quality and objectivity. During the various stages of the review and revision process, therefore, OTA encourages, and to the extent possible requires, authors to present balanced information and recognize divergent points of view.

Health Technology Case Study Series[a]

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18	The Efficacy and Cost Effectiveness of Psychotherapy; Leonard Saxe (Office of Technology Assessment) (OTA-BP-H-9(18))[d]
19	Assessment of Four Common X-Ray Procedures; Judith L. Wagner (OTA-BP-H-9(19))[e]
20	Mandatory Passive Restraint Systems in Automobiles: Issues and Evidence: Kenneth E. Warner (OTA-BP-H-15(20))[f]
21	Selected Telecommunications Devices for Hearing-Impaired Persons; Virginia W. Stern and Martha Ross Redden (OTA-BP-H-16(21))[g]
22	The Effectiveness and Costs of Alcoholism Treatment; Leonard Saxe, Denise Dougherty, Katharine Esty, and Michelle Fine (OTA-CS-H-22)
23	The Safety, Efficacy, and Cost Effectiveness of Therapeutic Apheresis; John C. Langenbrunner (Office of Technology Assessment)

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[b] Original publication numbers appear in parentheses.

[c] The first 17 cases in the *series* were 17 separately issued cases in *Background Paper #2: Case Studies of Medical Technologies,* prepared in conjunction with OTA's August 19&l report The *Implications of Cost-Effectiveness Analysis of Medical Technology.*

[d] Background Paper #3 to *The Implications of Cost-Effectiveness Analysis of Medical Technology.*

[e] Background Paper #s to The *Implications of Cost-Effectiveness Analysis of Medical Technology.*

[f] Background Paper #1 to OTA's May 1982 report *Technology and Handicapped People.*

[g] Background Paper #2 to *Technology and Hand"capped People.*

OTA Staff for Case Study #23

H. David Banta, Assistant ***Director, OTA***
Health and Life Sciences Division

Clyde J. Behney, ***Health Program Manager***

John C. Langenbrunner, ***Study Director***

Anne Kesselman Bums, ***Project Director***
Cynthia King, ***Analyst***
Pamela Simerly, ***Research Assistant***
Kerry Britten Kemp, ***Division Editor***

Virginia Cwalina, ***Administrative Assistant***
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President
Health Economics Research
Chestnut Hill., Mass.

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Washington, D.C.

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Urban Institute
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New York, N. Y.

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lnstitute for Health Policy Analysis
Washington, D. C.

Robert Sigmond
Blue Goss of Greater Philadelphia

Anne Somers
Department of Evironment and
Community and Family ***Medicine***
Rutgers University

Paul Torrens
UCLA School of Public Health

Keith Weikel
Group Vice President
AMI
McLean, Va.

Contents

Tables

Glossary

Air-emboli: A bubble of air obstructing a blood vessel.

Anaphylaxis: An unusual or exaggerated allergic reaction.

Antibodies: The chemicals in the human body's defense system that identify foreign substances, lock onto them, and trigger the body's immune attack on foreign substances. The body makes more than a million antibodies, each different and each capable of recognizing and attacking only one substance—one type virus, one type of bacteria, and so on.

Anticoagulant: Substances inhibiting normal blood clotting.

Antigen: A large molecule, usually a protein or carbohydrate, which when introduced in the body stimulates the production of an antibody that will react specifically with the antigen.

Atrophy: A wasting away; a diminution of the size of a cell, tissue, organ, or part.

Autoimmune: Directed against the body's own tissue. In autoimmune diseases, pathological antibodies are produced that attack the body's own normal tissue, such as kidney cells in glomerulonephritis or the nerve/muscle junction in myasthenia gravis.

Cost-benefit analysis (CBA): An analytical technique that compares the costs of a project or technological application to the resultant benefits, with both costs and benefits expressed by the same measure. This measure is nearly always monetary.

Cost-effectiveness analysis (CEA): An analytical technique that compares the costs of a project or of alternative projects to the resultant benefits, with costs and benefits/effectiveness expressed by different measures. Costs are usually expressed in dollars, but terms such as "lives saved, " "disability avoided, " "quality-adjusted life years saved," or any other relevant objectives. Also, when benefits/effectiveness are difficult to express in a common metric, they may be presented as an "array. "

CEA/CBA: A composite term referring to a family of analytical techniques that are employed to compare costs and benefits of programs or technologies. The terms as used in this case study means "cost-effectiveness analysis/cost-benefit analysis."

Cytapheresis: A type of therapeutic apheresis involving the selective removal of specific blood cells (red cells, white cells, and/or platelets).

Cytotoxic: A specific toxic action on cells of special organs.

Discounting: A procedure used in economic analysis to reduce to present value those costs and effects that occur in future years. Discounting is based on two premises: 1) individuals prefer to receive benefits today rather than in the future, and 2) resources invested today in alternative programs could earn a return over time.

Drug: Any chemical or biological substance that may be applied to, ingested by, or injected into humans, in order to prevent, treat, or diagnose disease or other medical conditions.

Effectiveness: Same as efficacy (see below) except that it refers to average or actual conditions of use.

Efficacy: The probability of benefit to individuals in a defined population from a medical technology applied for a given medical problem under ideal conditions of use.

Erythrocytapheresis: A type of cytapheresis involving the removal of red cells.

Extracorporeal: Outside the body, as in extracorporeal tubing for membrane apheresis equipment.

Glomerulonephritis: A variety of nephritis characterized by inflammation of the capillary loops in the glomeruli of the kidney.

Granulocytes: Any cell containing granules, especially a leukocyte containing certain types of granules in its cytoplasm.

Hemolysis: Separation of the hemoglobin from the red cells and its appearance in the plasma.

Hybridoma: A hybrid cell resulting from the fusion of two cells: a lymphocyte producing an antibody and a myeloma (or tumor cell), which grows well in culture and allows hybridoma to be established permanently. The antibodies from a given hybridoma are identical ("monoclinal").

Hyperviscosity: Excessive thickness of blood.

Hypocalcemia: Reduction of the blood calcium below normal.

Immune complexes: 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.

Immunoglobutin: A protein of animal origin endowed with known antibody activity. Immunoglobulins function as specific antibodies and are responsible for the humoral aspects of immunity. They are found in the serum and in other body fluids and tissues. There are five basic classes of immunoglobulins—IgA, IgD, IgE, IgG, and IgM.

Immunosuppressive: The artificial prevention or diminution of the immune response.

Incidence: In epidemiology, the number of cases of disease, infection, or some other event having its onset during a prescribed period of time, in relation to the unit of population in which it occurs. Incidence is a measure of morbidity or other events as they happen over a period of time.

Inpatient care: Care that includes an overnight stay in a medical facility.

Leukocytes: The white cells of blood.

Leukapheresis: A type of cytapheresis involving the reduction of excess white cells, as in leukemia.

Locke's solution: A solution of sodium chloride, calcium chloride, potassium chloride, sodium bicarbonate, and dextrose.

Lymphapheresis: A type of cytapheresis involving the removal of lymphocytes (certain white cells) without depletion of plasma components, making any plasma replacement, therefore, unnecessary.

Lymphocytes: A type of leukocyte, chiefly a product of lymphoid tissue, which participates in humoral and cell-mediated immunity.

Lymphokines: The biologically active soluble factor produced by white blood cells.

Lyrnphoplasmapheresis: A type of cytapheresis involving a combination of lymphopheresis and plasmapheresis: the removal of both lymphocytes and plasma, usually during a single procedure, and requiring the use of replacement fluids.

Medicaid: A Federal program that is administered and operated individually by each participating State government that provides medical benefits to certain low-income persons in need of health and medical care.

Medical technology: The drugs, devices, and medical and surgical procedures used in medical care.

Medicare: A nationwide, federally administered health insurance program authorized in 1965 to cover the cost of hospitalization, medical care, and some related services for eligible persons over age 65, persons receiving Social Security Disability Insurance payments for 2 years, and persons with end-stage renal disease. Medicare consists of two separate but coordinated programs—hospital insurance (Part A) and supplementary medical insurance (Part B). Health insurance protection is available to insured persons without regard to income.

Monoclinal antibodies: Antibodies derived from a single source or clone of cells which recognize only one kind of antigen.

Myeloma: A malignant disease in which tumor cells of the antibody-producing system synthesize excessive amounts of specific proteins.

Outpatient care: Care that does not include an overnight stay in the facility in which care is provided.

Paraproteinemias: Presence in the blood of a paraprotein (immunoglobulin produced by a clone of neoplastic plasma cells proliferating abnormally), such as a cryoglobulin or a macroglobulin, in amounts not normally observed.

Pathogen: A specific causative agent of disease.

Plasma: The fluid portion of blood in which particulate components are suspended.

Plasma exchange: An often used therapeutic application of apheresis, in which 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, plasma substitute, or combination of albumin, calcium, and normal saline, depending on the need of the individual patient. Some researchers 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. Although the plasma replacement in early cases was initiated only for purposes of expansion of the blood vessel "intravascular" volume, later investigators 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.

Plasma perfusion: A multiple separation technique in therapeutic apheresis whereby the patient's plasma is first isolated from the cellular elements and subsequently passed through a filtration medium (either absorptive columns or membranes) to remove unwanted plasma components. The filtered plasma is then returned to the patient along with the cells.

Plasmapheresis: Strictly defined, a type of apheresis that 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, and it has been traditionally found in blood banks and in the plasma collection industry.

Platelets: Oval-shaped structures found in the blood of all mammals and chiefly known for their role in blood coagulation.

Plateletapheresis: A type of cytapheresis involving the reduction of abnormally high levels of platelets.

Prevalence: In epidemiology, the number of cases or disease, infected persons, or persons with disabilities or some other condition present at a particular time, in relation to the size of the population. Prevalence is a measure of morbidity at a point in time.

Proteins: The functional and structural components of cells.

Purpura: A group of disorders characterized by purplish or brownish-red discoloration, easily visible through the epidermis, caused by hemorrhage into the tissues.

Randomized clinical trial (RCT): An experimental design involving the random assignment of human subjects either to an experimental group (in which subjects receive the treatment being studied) or to a control group (in which subjects do not receive the treatment being studied). Also referred to as "randomized controlled clinical trial" or "controlled clinical trial."

Registry: The collection of health or medically related data typically abstracted from a specific document (e.g., medical record or death certificate) using cri-

teria that are applied retrospectively. In practical terms, registries generally cover discrete political or geographic areas.

Reliability: A measure of the consistency of a method in producing results. A reliable test gives the same results when applied more than once under the same conditions. Also called "precision. "

Remission: Abatement or diminution of the symptoms of a disease.

Risk: A measure of the probability of an adverse or untoward outcome and the severity of the resultant harm to health of individuals in a defined population and associated with use of a medical technology applied for a given medical problem under specified conditions of use.

Safety: A judgment of the acceptability of risk (see above) in a specified situation.

Technology: **The application of organized knowledge to practical ends.**

Technology assessment: A comprehensive form of policy research that examines the technical, economic, and social consequences of technological applications. It is especially concerned with unintended, indirect, or delayed social impacts. In health policy, the term has also come to mean any form of policy analysis concerned with medical technology, especially the evaluation of efficacy and safety. The comprehensive form of technology assessment is then termed "comprehensive technology assessment ."

Validity: A measure of the extent to which an observed situation reflects the "true" situation. *Internal validity* is a measure of the extent to which study results reflect the true relationship of a "risk factor" (e.g., treatment or technology) to the outcome of interest in study subjects. *External validity* is a measure of the extent to which study results can be generalized to the population that is represented by individuals in the study, assuming that the characteristics of that population are accurately specified.

Vasculitis: Inflammation of a blood vessel.

1.

Introduction and Summary

Introduction and Summary

BACKGROUND AND SCOPE OF THE CASE STUDY

For several centuries, one of the chief therapeutic methods besides the administration of herbs was to attempt to remove noxious substances from the body—either by a general purging, often with drastic laxatives, or still more dramatically, by bloodletting. It has been said that several important persons, Louis XIII of France and George Washington, for instance, were probably killed by such therapy (43,137).

In the past decade, the medical community has increasingly used therapeutic apheresis, * a technology* * initially mindful of the ancient practice of bloodletting. In therapeutic apheresis, a patient's plasma and/or blood cellular parts are separated and then removed from the blood and replaced by substitute plasma or a related physiological solution. It is believed that abnormal or harmful substances or cells are thereby removed, leading to a cure or arrest of the disease. Results reported in the scientific literature have been dramatic, and apheresis is being used to treat an increasing number of medical conditions. Skepticism over the validity of such claims and also the high costs of apheresis, however, have touched off recent controversies over this procedure's use.

Therapeutic apheresis is not a new procedure but the extent of its use has grown, and may continue to grow, substantially and rapidly. From **1977 through 1980, procedure volume increased** more than 500 percent, from around 5,000 to over **40,000 procedures per year (108). These estimates were developed retrospectively, because there has been no formal reporting system. In the late 1970's, the rate of growth far outpaced the estimates. The now defunct National Center for Health Care Technology, for example, originally estimated use in 1979 at "hundreds of procedures, " only to learn later that the actual procedure volume that year hovered around 16,000 (34). This phenomenal rate of growth between 1977 and 1980 led in turn to general estimates of a half million procedures per year by 1985. Very recently, however, these estimates have been revised downward because of increased concern by health care professionals and third-party payers alike over the technology's safety, effectiveness, and costs (35).**

At present, apheresis is primarily accepted as an acute therapy in a small group of relatively obscure diseases, and the number of patients undergoing treatment totals approximately **20,000 (70). Like another new technology of recent years, the computer, therapeutic apheresis might in some respects be characterized as a "solution looking for problems." This is evidenced by the fact that apheresis is being evaluated as a chronic treatment modality for several major diseases, including rheumatoid arthritis, multiple sclerosis, and certain forms of cancer. These disorders represent a potential patient population of hundreds of thousands of cases in this country. Because patient benefits for these disorders have often** been only partial, temporary, or equivocal, the emergence of efficacy and, especially, cost concerns is not surprising.

The costs of apheresis have, in fact, become a particularly volatile issue. Therapeutic apheresis may be found to have great potential for reducing illness and death. The potential number of medical conditions and size of the patient population that could be covered, in combination with the costs of apheresis treatment ($400 to $1,200

● There is some debate over the proper terms for the procedures described in this case study. The term "plasmapheresis" has been used in the medical literature since ***1914.*** Some argue that the more technically correct and appropriate noun to describe the separation and removal of blood components is "apheresis" (see, e.g., ***67).*** In any case, the reader should be aware that the terms "plasmapheresis" and "apheresis" are used rather interchangeably in the literature as well as in common usage ***(73).***

● *The Office of Technology Assessment (OTA) defines technology as the practical application of organized knowledge. The term ***medical technology,*** as used in this case study, is a drug, device, or medical or surgical procedure used in medical care. (The term may also apply to the organizational and supportive systems within which medical care is delivered, but those systems are not the focus of this case study.) ***(95).***

per treatment, with a significant number of treatments needed per patient), however, point to a possibly vast expenditure of funds on apheresis—in the billions of dollars. This cost issue has been further highlighted because some Americans already question the resource expenditures of over $1 billion per year for each of three established therapies: coronary bypass surgery, kidney dialysis and transplants, and treatment of newborns in neonatal intensive care units **(2).**

Major market opportunities for equipment, supplies, and services have been forecast for apheresis technology in the next decade. As a result, therapeutic apheresis has been the subject of investor interest and increased industry participation. Vigorous research, development, and marketing activities have been undertaken by companies in the United States, Europe, and Japan. Major American participants include Haemonetics Corp., International Business Machines (IBM), Baxter Travenol, Cobe Laboratories, Parker-Hannifin, Cordis-Dow, and Millipore Corp. These companies have developed several new therapeutic techniques in response to perceptions of a need to reduce present costs. These techniques are discussed in later chapters, although a description or analysis of the industry or market that has developed around the technology of therapeutic apheresis is beyond the scope of this study.

This case study was prepared as part of OTA's project on "Medical Technology and Costs of the Medicare Program." The entire project is being conducted in response to requests by the House Committee on Energy and Commerce and its Subcommittee on Health, and the Subcommittee on Health of the Senate Committee on Finance. This particular portion of the project responds to a specific request by the Senate Finance Committee's Subcommittee on Health for scientifically based information on the effectiveness of therapeutic apheresis.

SUMMARY

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 or its symptoms. The procedure can take several forms, though it 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. Just as in 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.

The idea of apheresis first originated in 1914, but it was not until World War II that human apheresis was considered and used as a means of meeting the increased demand for plasma. 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. The first successful *therapeutic*** use of apheresis was reported in the late 1950's, and during the next few years, reports appeared on the application of apheresis to several diseases. Recent advances during the past decade in basic research, in equipment, and in the technique of apheresis have provided a rationale for carrying out apheresis on a much larger scale and in a wider variety of diseases. 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.

The rationale for performing apheresis is to remove one or more components of blood that conceivably contain and carry pathogenic substances linked to a patient's disease process. Various diseases have been increasingly associated with these "abnormal" blood components in the circulation, and these components are believed to

● **A** number of the scientific **and medical** terms used in this case study are defined in the Glossary,

initiate or aggravate the disease condition. Apheresis typically has been used in diseases involving excessive levels of three main types of substances found in blood components: plasma protein, antibodies, and immune complexes. 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. The volume and frequency of blood component exchanges have not been well established, and for the most part, benefits remain anecdotal and difficult to reproduce. Effects of therapeutic apheresis are not generally believed to be curative, but are usually of a temporary nature. Often the procedure is used in conjunction with other treatments, especially drug therapy.

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, although it appears that this trend may be moderating.

Approximately 5 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. For most apheresis procedures, however, automated centrifuge equipment is used. Some new major developments in hardware, including adsorption columns and semipermeable membranes that function as molecular sieves, are now either undergoing clinical tests or about to be marketed for general use. These advances in equipment may, in the course of the next decade, be improved or even overshadowed by advances in basic biomedical research or by emerging developments such as biotechnology.

Scientific and Medical Aspects of Apheresis: Issues and Evidence

By almost any standard, treatment by apheresis is still in relatively early stages of development—there are no ideal protocols based on a complete understanding of reasons for its efficacy. * As a result, much of the existing literature on the effectiveness of apheresis is not of very good methodological quality. The great majority of the reported studies are case reports without any conclusive control groups, blinding, randomization, or other techniques used in controlled clinical trials. Even if standardized protocols could be developed, scientific research on the effectiveness of apheresis might be difficult or undesirable to conduct. Ethical and practical problems have hindered the implementation of randomized clinical trials and other controlled research. Furthermore, the assessment of individual treatments is difficult because apheresis procedures are often provided in combination with drug therapy or other treatment regimens.

Measures of outcome have been a recurring critical issue, as well, because such measures have varied enormously, both across and within disease indications. Outcome measures have sometimes focused on improvement in clinical signs and symptoms, other times focused on biologic and chemical parameters, and in other instances been lacking, not specified, or ill-defined. The reliability and validity** of outcome measures are also problematic because of the nature of several illnesses treated by apheresis which are characterized by abrupt and pronounced changes that may or may not be attributable to therapeutic effects.

Finally, the interpretation of many studies of apheresis that are available is hindered because only particular types of patients, i.e., the "worst cases, " tend to receive apheresis treatments (as a last resort after other conventional therapies fail). Because of these various limitations of the available research evidence, indications about the safety, efficacy, and effectiveness of apheresis are necessarily limited. Nevertheless, some tentative conclusions and directions for treatment can be discerned.

*'Efficacy** is the health benefit as measured under controlled conditions such as those in a randomized clinical trial. *Effectiveness* is the health benefit as measured under average conditions of use.

'Reliability is a measure of consistency of a method in producing results. A reliable test gives the same results when applied more than once under the same conditions. *Validity* is a measure of the extent to which a situation that is observed in a study is reflective of the true situation.

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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. Apheresis device equipment can also be termed effective in the sense that the technology accomplishes the intended removal of plasma and cells. However, there is very little definitive evidence documenting the widespread success of the technology in actually improving health. 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 (Waldenstrom'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 with other specific disease conditions. Convincing proof of clinical efficacy, however, is still lacking in the wider variety of diseases in which this treatment is being used.

Large prospective randomized trials, many of them funded by the National Institutes of Health, have been organized for several disease applications in which apheresis therapy has been used, in order to more precisely define what advantages, if any, these treatments may have. Further research will be needed to both compare present treatment approaches with new and emerging blood filtration methods and to test related scientific advances (e.g., the use of monoclinal antibodies).

Cost Effectiveness and Reimbursement Policy: Issues and Evidence

In addition to the issues of health status or other health outcome related effects (i.e., safety, efficacy, and effectiveness) of apheresis, efficiency issues must also be addressed. Two important methods used to assess the costs and benefits of therapeutic apheresis, and develop comparisons among effects, costs, and benefits are cost-benefit analysis (CBA) and cost-effectiveness analysis (CEA). CBA is used to develop comparisons of the benefits of treatments against the resources they consume, with both benefits and costs expressed in dollars. It is difficult to conduct a CBA for apheresis, because even though the therapy has reportedly lessened suffering and helped prolong lives, reliable estimates of these benefits have yet to be determined and quantified. CEAs are used to evaluate the relative cost of alternative treatments per unit of effectiveness (typically specified in nonmonetary terms). CEAs for apheresis have not yet been conducted because sufficient data on outcomes for apheresis and alternative treatments are lacking.

Nevertheless, the task of evaluating treatments can include the context of costs, for which there have been several general estimates. National expenditure estimates on apheresis therapy, which is currently performed on only selected patients, range from **$3.2 million to $240 million. If, however, apheresis therapy is extended in the future to the wider array of diseases to which it has been only experimentally applied thus far, total treatment costs could range from $650 million to over $7 billion per year.**

Third-party payment will bean important influence on future adoption, use, and economic effects of therapeutic apheresis, through the funding and reimbursement policies of both private and government insurance programs. Reimbursement policies, like other aspects of therapeutic apheresis, have been the subject of some debate because of the competing factors of cost and therapeutic promise. The development of most of these policies has been recent. On September 15, 1981, the Health Care Financing Administration issued its first national instructions for apheresis, announcing coverage under the Medicare Program for only a small group of relatively rare disease indications.* Medicaid coverage regulations vary from State to State because of changes in Federal funding policies, which provide States with some latitude in deciding how Federal funds are spent. Other governmental programs, such as the Department of Defense's CHAMPUS, as well as pri-

● On Apr. 20, 1983, Public Law 98-21 provided for extensive changes in Medicare reimbursement policies for hospital-based care. Under the statute, whose provisions will be phased in over 3 years, hospitals will receive a flat fee per patient, set prospectively, on the basis of patient diagnosis in one or more of 467 diagnosis-related groups (DRGs). It is unclear at this point how the DRG-based payment system will affect the adoption and use of apheresis. What is certain, however, is that information on the effectiveness of this treatment will be even more important as physicians and patients face increasingly scarce resources.

vate medical insurers, also vary on which disease indications should be covered, probably stemming from a less than consistent scrutiny of the evidence on safety and efficacy. A widening of Medicare and private insurer coverage of therapeutic apheresis for specific life-threatening complications (e.g., rheumatoid vasculitis) is probable in the near future. But direct cost estimates and the potential cost of possibly premature diffusion alone make it unlikely and unwise that third-party payers will support any broad extension of benefits for apheresis treatment until more valid data is generated. Until evidence is available, therapeutic apheresis will largely be viewed as an experimental technique, not to be considered as a part of routine care. In light of such a situation, present research and clinical trials being carried out assume even greater importance.

Implications for Policy

Several recurring issues in need of further study or resolution arise during an examination of apheresis technology. One issue, which arises because the technology is still in the development stage, is what the appropriate patient criteria for use are, what the appropriate timing of intervention in the course of a disease is, and whether the procedure to be followed in performing therapeutic apheresis is adequately standardized. Such questions are basic in the development of a technology, and research to address these questions is needed, as it forms a necessary foundation for the conduct of well-controlled testing and clinical trials. Interim apheresis registries could track conditions of use and forma knowledge base for development of well-controlled studies.

A second issue, which arises where conditions of use have been sufficiently standardized, is the lack of and need for well-designed clinical trials of apheresis. There has been a recent infusion of government and foundation funding to offset the high costs of such trials. Should costs continue to be a problem, one alternative might be to have third-party payers, including Medicare, selectively reimburse for therapeutic apheresis in return for clinical data. If implemented properly, this alternative could substantially increase the quality of information available for public and private reimbursement coverage decisions. Evidence of the technology's cost effectiveness could result in yielding substantial budgetary savings. Even if the results of such trials were disappointing, they could lead the way to unexpected advances in research.

A third issue is the possibly transitional nature of apheresis technology. Advances in apheresis equipment, advances in related areas of basic biomedical research, and emerging parallel developments such as biotechnology, indicate that policies affecting therapeutic apheresis must be considered in the larger context of present scientific and technological flux. Considerable attention will be needed to establish the most rational and productive balance between development and support of apheresis technology and that of basic and applied research toward other technologies of similar or more favorable promise.

ORGANIZATION OF THE CASE STUDY

This case study is organized into five chapters. **Chapter 2 provides definitions and descriptions of the various types of apheresis technology, along with perspectives on the history and etiology of** apheresis use. It also describes the current treatment process and future trends, especially as they involve changes in apheresis equipment devices.

Chapter **3 reviews research on the scientific and medical aspects of therapeutic apheresis. Included is a description of methodological issues involved in therapeutic apheresis evaluation.** The evidence on the safety, efficacy, and effectiveness of the procedure for the wide range of specific diseases and conditions is examined. The results of three

methodological reviews of therapeutic apheresis for treatment of hemolytic uremic syndrome, acquired Factor-VIII inhibitor, and Guillain-Barre syndrome, prepared for this case study, are also discussed. (The full reviews are presented as apps. B, C, and D.)

Chapter 4 focuses on reimbursement and cost-effectiveness issues. Data and estimates on the costs and benefits of providing therapeutic apheresis and policy issues of the current system are considered in relation to safety and efficacy data regarding treatment. In chapter 5, implications for policy are provided in light of several recurring issues that emerge from an assessment of this technology.

There are six appendixes to this case study. Appendix A acknowledges the valuable assistance of the Health Program Advisory Committee and several other individuals for their review and advice in putting together this report. Appendixes B, C, and D contain the previously mentioned methodological reviews, while appendix E briefly discusses the cause and pathological development of autoimmune diseases. A full bibliography of the scientific literature on therapeutic apheresis, compiled by the American Red Cross and organized by disease categories, is included in appendix F. (The bibliography specific to this case study can be found in the References section following the appendixes.)

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.

3 Scientific and Medical Aspects of Apheresis: Issues and Evidence

3. Scientific and Medical Aspects of Apheresis: Issues and Evidence

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' is even today, however, often based on unsystematically collected data. Because of the 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.

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).**

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 nontreatment 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 maybe 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 pretreatment 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 comeasures 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 lo-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 general**ities. 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, * 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.

● 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 ***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)[b]	Sickle cell Polycythemia
Rheumatology		—	Rheumatoid arthritis (RA)[a] Systemic lupus erythematosus (SLE) Scleroderma Other	Rheumatoid arthritis
Neurology		Guillain-Barré syndrome (GBS) Myasthenia gravis (MG) Multiple sclerosis (MS)[a] Polymyositis		Multiple sclerosis
Oncology	Multiple myeloma		Other cancers	Some leukemias
Nephrology	—	Transplant rejection Goodpasture's syndrome (GS)	Progressive nephritis Glomerulonephritis	
Other	Toxins Poisons Hypercholesterolemia Thyroxtoxicosis Primary biliary cirrhosis Hypertriglyceridemia			

[a]Preferred apheresis therapy not yet decided; clinical studies have employed plasmapheresis, Plasma exchange, lymphapheresis, and/or lymphoplasmapheresis.
[b]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 necrologic 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 hypercholesteroleznia*** 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 necrologic 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 ***amyotropic 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 lymphoplasmapheresis. 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 approximatelys million to 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 "procedures 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 lymphoplasmapheresis 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 anecdotal and awaits additional research before reliable conclusions can be drawn regarding the potential role of apheresis for these disorders (42,80,108,144).

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

Miscellaneous immunological diseases
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.

Cell-Related Diseases

The use of apheresis (specifically cytapheresis) 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, cytapheresis 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 (Waldenstrom'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 monoclinal 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
Major NIH Stud/as		
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, xanthomatosus, 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
Other major studies		
Rogosin 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

4
Cost Effectiveness and Reimbursement Policy: Issues and Evidence

4. Cost Effectiveness and Reimbursement Policy: Issues and Evidence

In addition to the issues of health status or other health outcome related effects (i.e., safety, efficacy, and effectiveness) of apheresis, efficiency issues must also be addressed. The cost of providing apheresis therapy is a matter of almost universal concern in the available literature. As spiraling health care costs continue to plague medical care delivery in this country and elsewhere, it is important to examine whether there is improvement in the quality of life and which therapies offer the greatest value for the resources invested.

Because of the broad and pervasive influence of third-party payment mechanisms on health care delivery, any discussion of economic effects of therapeutic apheresis must also be closely tied to an examination of funding and reimbursement policies of both private and government insurance programs. Reimbursement policies have profound effects on the adoption and use of medical technologies, as well as the innovation process itself of medical procedures such as therapeutic apheresis. Informed coverage decisions require information concerning medical technologies, that is at least as detailed as that needed for the regulatory decisions of the Food and Drug Administration (FDA) regarding device equipment. Whereas regulatory decisions tend to be of a "go", "no go" nature, reimbursement decisions are, or at least could be, more related to ***appropriate*** use of technologies, a much finer distinction (104). Appropriate use decisions would support the provision of effective apheresis therapy and efficient care. That is, only proven treatment alternatives would be considered for widespread clinical application and the lower cost treatment alternative would not only be available but used (102,104).

Until recently, apheresis was routinely reimbursed for by some third parties when prescribed by a physician. However, concerned about costs and estimates of expansion of use over the next 5 years, third-party payers are now attempting to tailor their policies according to the principle of appropriate use—i.e., to pay for apheresis where and when it is a proven and efficient therapeutic method **(80,117). Medical insurers are, however, far from a consensus on how, when, and if they should cover apheresis (34,49).**

The research and policy issues regarding the costs and benefits of apheresis therapy, including a discussion of third-party reimbursement, form the substance of this chapter. It is a discussion that initially examines the methods that can be used in assessing the economic effects of therapeutic apheresis. Currently, the most visible and potentially most useful of methods is cost-effectiveness analysis (CEA). As CEA is not simply an economic technique, but rather a blend of economic and clinical information, it will serve to conceptually integrate cost concerns with the assessment of safety and efficacy issues in chapter 3. An absence of reliable estimates of the efficacy and safety of apheresis treatment and of its costs and savings prohibits conclusive results, but gaps in present knowledge can be identified and directions for future research can be addressed.

COST EFFECTIVENESS

Two important methods used to assess the costs and benefits of therapeutic apheresis, and developing comparisons among effects, costs, and benefits are cost-benefit analysis (CBA) and cost-effectiveness analysis (CEA). CEA implies a comparative analysis of the costs and health effects of alternative treatments. In a CEA, a common outcome is specified (e.g., functional status) and the costs

of providing alternative treatments are compared. Treatment costs are typically specified in monetary terms. CBA, on the other hand, requires that both cost and benefits be assigned monetary values. A CBA examines the ratio of resources used (cost) to resources saved (benefits) when particular treatments or even different treatment regimens *or* programs are employed (102, 104).

While CEA/CBA can be thought of as an aid to synthesis of both health effects and economic effects, the value of a CEA/CBA lies more in the process of performing the analysis than in any numerical results. There are a number of reasons for this, among the most important of which are CEA/CBA's inabilities to adequately address ethical issues and the uncertainty of specifying comprehensively the costs and benefits of alternative treatments. This is clearly the case with therapeutic apheresis because there are no reliable estimates of savings due to treatment benefits that are available or known. In addition, factors other than those qualified in a CEA/CBA (e.g., social, ethical, or value influences) should be considered in making a decision **(12,98,102,104).**

OTA, in its assessment of the methods of CEA/CBA (98) developed 10 principles to guide the conduct, use or evaluation of CEA/CBA studies (see table 6). The Principles most relevant to the assessment of therapeutic apheresis are that alternative means (technologies) to accomplish the stated objectives should be identified and subjected to analyses; all foreseeable benefits/effects should be defined and, if possible, measured, as should all expected costs; present value discounting should be performed; sensitivity analyses should be conducted to show a range of possible outcome values; and ethical issues (that have surfaced in significant ways in therapeutic apheresis) should be addressed. The rigorous specification of data sources for quantitative analyses was another important criterion for CBAS.

Table 6.—Ten General Principles of Analysis (for CEA/CBA Methodology)

1. Define probiem
2. State objectives
3. identify alternatives
4. Analyze benefits/effects
5. Analyze costs
6. Differentiate perspective of analysis
7. Perform discounting
8. Analyze uncertainties
9. Address ethical issues
10. Interpret results

SOURCE: Office of Technology Assessment, 1980.

Potential costs and benefits can be assessed with varying degrees of comprehensiveness. Further, means for estimating them vary **(102,104).** Thus, in a CBA, the cost of a treatment procedure includes not only the direct costs of salaries of treatment providers and support staff, disposable, replacement fluids, drug therapies, administrative and overhead costs, but also indirect costs such as lost productivity due to patient's time missed in work. Additionally, it should be noted that uncritical use of market prices can lead to large gaps between cost estimates and true costs. Illustrative of this problem is the use of hospital charge data to reflect the costs of hospital care. A common practice, this form of "pricing" ignores the known idiosyncrasies of hospital accounting in which hospitals charge well above true marginal costs for certain services and *use* the profits to subsidize other services for which charges do not cover marginal costs. For example, hospital pharmacy charges can vary from 10 to 1,000 percent of the true cost of drugs depending on the frequency of their use, their level of cost, purpose, etc. **(104).** In the case of apheresis therapy, replacement fluids such as albumin, saline solutions, and fresh frozen plasma are particularly vulnerable to such pricing practices. For example, a recent survey by Levy (74) of Los Angeles hospitals showed almost all paid $28 to $29 for one unit of albumin. In turn, these hospitals charged the patient any where from a low price of **$90 to** a high of $175 per unit.

In conducting a CBA *or CEA* one must decide which benefits to measure and how to measure them, if measurement is at all possible. For example, it has been argued that substantial savings from reduced expenditures on drugs, surgery, and hospitalization accrue from therapeutic apheresis treatments, although this will vary depending on the differing lengths and intensity of the disease remission.

Unemployment and lost productivity could be reduced in the long-term as well. Limiting analyses

to work-related measures, however, may have the effect of underestimating the potential benefits of apheresis therapy to a significant number of individuals not currently in the work force—e.g., the chronically ill, the retired elderly, students, full-time homemakers, etc. A further point is that the efficiency of apheresis may decline—as evidenced by frequent usage as a treatment of last resort—with severity of impairment. In addition, savings on such items as reduced expenditures for quack remedies need to be calculated. It is reported that rheumatoid arthritis patients, for example, spend over $1 billion a year on purported remedies ranging from the "night shade diet," which prohibits tomatoes, eggplant, and potatoes, to devices such as vibrators and drugs such as DMSO (dimethyl sulfoxide). Some arthritic sufferers even sit in uranium mines in their search for relief (34). Other benefits, such as the sense of well-being that apheresis reportedly generates in many patients **(108),** may be more difficult to quantify.

Despite problems, when it is done well, the use of CEA / CBA does aid the complete listing of expected costs and benefits as well as the explicit consideration of assumptions underlying them. Assuming such specification is possible, such analyses provide a better scientific basis to aid in making decisions. Given the current debate over the relative costs and benefits of apheresis, and the increasing debate over reimbursement policy, such information does indeed appear to be essential.

Estimating Costs

While no reliable estimates of savings due to treatment benefits are available or generally known (12), the present task of evaluating treatments can include the context of costs, for which there have been several general estimates. There has additionally been a more specific study concerning the costs of reimbursing for apheresis of rheumatoid arthritis patients under the Medicare program.

By almost any standard, the costs of providing this therapy are a concern. It is the issue of costs that has aroused the greatest controversy surrounding the technology and is the most obvious explanation for the increasing scrutiny of apheresis by a variety of health care professionals. The concerns over costs have focused not only on the price of a single treatment session, but also the dramatically rising use of apheresis for therapeutic purposes in recent years.

Calculations

There are two dimensions (124) to expenditure determination-price and quantity. Many technologies become expensive because of high cost even when applied to a small number of patients (e.g., end stage renal disease), while others generate large expenditures because the procedure is so extensively used even though the cost per patient is relatively low (e.g., routine in-hospital lab tests). Apheresis represents an interesting combination of a technology which is, on the one hand, extremely expensive per patient, but is simultaneously of potential benefit to great numbers of patients.

Simple cost projections for therapeutic apheresis can be said to depend on three variables: the price of each unit of service (cost per treatment), the quantity of services that would be used (treatments per patient), and the size of the population potentially benefiting from treatment (patient populations). By multiplying these variables together, an estimate of total expenditures can then be determined.

Cost per Treatment

Estimates of the costs of individual apheresis treatments are very much available, but vary widely according to individual author and analysis from $400 to $1,200. (A midpoint estimate, then, is $800 per treatment.) An investment of $19,000 to $32,000 for a blood cell separator is the initial cost here, and disposable sets produced by manufacturers will vary between $40 and $90 per treatment. (Membrane disposable prices may be substantially higher—as much as $400-at first.) Space (overhead expense), trained staff, and a physician-director are also essential ($27 to $300). Replacement fluids (at an average volume of **2.8** liters), such as albumin or fresh frozen plasma, make up the remainder of the costs, running **$125** to **$600** per treatment (the exception is cytapheresis, which usually does not require re-

placement proteins because volume loss is small) (2,8,12,22,34,42,108,117,75,125) .

Treatments per Patient

Most studies estimate the number of treatments per patient as averaging about 10 per year, though a few estimate that number to be as low ass and as high as 15 to 20 per year. As already discussed, apheresis protocols for various diseases will differ dramatically in number and frequency of treatments. Some applications will entail single treatments for emergencies, while it is likely that chronic diseases such as rheumatoid arthritis will generally require 15 to 20 treatments, although more than 30 will be used in some cases **(2,34,73, 108,42,117).**

Patient Populations

The potential patient population for apheresis can be appreciated in a number of different ways. If the potential patient population is defined as those persons with any of more than 75 diseases currently treated with apheresis, the potential population is significant. There are an estimated 5 million to 7 million people with rheumatoid arthritis, 400,000 to 500,000 persons with multiple sclerosis, 400,000 to 500,000 persons with systemic lupus erythematosus, 100,000 myasthenia gravis patients, and at least **50,000 to 60,000 others** with one of the other diseases. However, many patients in each disease category are presently being treated satisfactorily with drug therapy, and thus they may not now be considered candidates for apheresis (though in some diseases, such as multiple sclerosis and Goodpasture's syndrome, effective alternative therapy is very limited, so that virtually the entire patient population could eventually become candidates for apheresis). If apheresis is used only on patients who have failed to respond to traditional forms of therapy, the potential total patient population is reduced to about 5 percent. of its original size, and estimates place this population at from **325,000 to 427,000 (22,34,73,80,117,125).** These must be considered conservative estimates because they limit the potential candidate population to those patients who have reached a severely debilitating or life-threatening state in these disease states. If apheresis therapy replaces other therapy modes in routine maintenance programs for various disorders, the patient population would be much higher (117).

Results

Having determined estimates for each of these several variables, and multiplying these variables together, total cost estimates for apheresis therapy per year can be projected to range from $650 million to $7.69 billion, with a midpoint estimate of $3.01 billion (see table 7). Importantly, these pm-***jections are simple cost calculations that carry with them a number of methodological caveats.***

Caveats

For one, there are no cost calculations of accompanying hospitalization, ancillary services or essential adjuvant therapies, such as immunosuppressive drugs, which would increase cost estimates. Secondly, there is no determination here of "adoption share, " a yearly measure of market penetration, defined as the proportion of eligible candidates for which treatment was indicated and on which it would have actually been performed. Calculation of the adoption share requires fairly accurate procedural use data, as well as projecting what the diffusion rate for the procedure is

Table 7.—Estimating Costs of Apheresis Therapy

	High estimate	Midpoint	Low estimate
Costs per treatment	$1,200	$800	$400
Treatments per year	15	10	5
Patient population	427,000	376,000	325,000
Total costs	$7.69 billion	$3.01 billion	$650 million

SOURCE: Off Ice of Technology Assessment, 1983.

and will be. * Prediction of adoption share is one of the most difficult tasks, but one of the most important for predicting future costs. The adoption share subsequently allows for the discounting back of future costs over a determined patient care time horizon, and the accumulation of a present value.

Currently, apheresis is performed on only selected patients. Unfortunately, no accurate data exists on national figures, with estimates placing the number of procedures performed at from 80,000 to 200,000 per year (22,34,73,80,117). These estimates, if accurate, would mean that, using OTA treatment estimates (see table 7), current national expenditures on apheresis range from $3.2 million to $240 million. According to Schweitzer and Foxman (124), however, if one assumes availability of reimbursement for this therapy, then one must also assume expansion of availability of service, and utilization would increase over time to essentially the point where all who could derive benefit from treatment would do so. The importance of reimbursement policies covering apheresis becomes apparent, then, if such policies push the adoption share to 100 percent. Given present reimbursement policies (see section on "Third-Party Reimbursement"), this represents an extreme estimate but is useful for cost purposes here.

The economic and cost implications of a decision by a third-party payer to reimburse for apheresis is a last but crucial caveat to cost estimates. As Schweitzer and Foxman (124) further point out, if medical services were not linked to one another, and criteria determining appropriateness or need for a service were unambiguous, the relationship between reimbursement and expenditure would be a simple one. Under these conditions, one would simply identify the quantity and price of the service in question prior to a change in the reimbursement policy, and assume that these expenditures would be shifted to the new payer. However, both the demand for and the supply of medical care are price sensitive. A decision to reimburse, by lowering the net price to consumers and raising it to those who produce medical care—physicians and hospitals—will, therefore, have a tendency to increase the quantity of the service consumed. In addition, price effects will arise involving not only the service in question, but other services which are either substitutes for or complements to it. Failure to fully appreciate these quantity and price effects contributed to the serious underestimate of the End-Stage Renal Dialysis program in 1972 (113).

Cost Studies

Only one known study, prepared under contract to the National Center for Health Care Technology (NCHCT) in 1981, has systematically examined the costs of apheresis. The study only estimated savings, if any, anticipated as a result of the disapproval of coverage for a medical procedure. The study was carried out following NCHCT's recommendation to the Health Care Financing Administration (HCFA) not to reimburse for therapeutic apheresis in the treatment of rheumatoid arthritis. The cost projections, by most sensibilities, were considered startling. The study used a Wallace, et al. (140), estimate that as many as 700,000 Americans might be candidates for apheresis at a first-year cost of $40,000 per patient and $18,000 per patient each year thereafter. This implied a cost of up to $28 billion in the first year. If 5 to 10 percent of the nearly 1 million Medicare-eligible patients with rheumatoid arthritis were to be given apheresis, it would cost between $2 billion and $4 billion (124). NCHCT noted that these were gross cost projections, and could be modified by projected savings from reduced expenditures for hospitalized bed rest, medication, and joint surgery. Maintenance of, or return to, a productive lifestyle would also have to be considered (as noted previously in this section) if apheresis were shown to be effective (107).

● The classical pattern of diffusion has been the ascending logistic curve, which indicates that the proportion of adopters for a new technology rises with time according to an S-shaped pattern. This pattern is appropriate for technologies for which continued ascendency is likely over the immediate horizon, and for which subsequent high utilization can be expected. For many applications of apheresis, however, the pattern is probably more complex. Warner (141) has proposed a three-stage "desperation-reaction" model of medical diffusion, in which initial enthusiasm is followed in the second stage by an adjustment, followed subsequently by informed decisions. The informed decisions could represent mature, high use (as in accepted innovation) or zero use (for an unacceptable innovation). Furthermore, disapproval of reimbursernent could occur at any point in this process (19).

The NCHCT study of potential costs, by comparison, casts OTA cost estimates as conservative, both from the standpoint of potential patient population and cost per treatment estimates. **The NCHCT study,** however, has been criticized for **usage** of "inflated" estimates pertaining to potential patient population. More widely accepted figures come from **Max** Hamburger, in concurrence with the American Society for Apheresis (49), who estimates the potential RA patient population at less than **70,000,** or about 10 percent of NCHCT estimates.

Regardless of which estimate is selected, the effect of reimbursement policy on potential direct expenditure estimates is clear from both studies. Furthermore, as alluded to earlier, the expenditure implications of a reimbursement decision are intertwined with the technology's diffusion, producing direct and indirect effects, some of which may be wide-reaching. The magnitude of the direct cost estimates alone suggests that the procedure's safety and efficacy should be closely scrutinized because of the potential cost of possibly premature diffusion.

THIRD-PARTY REIMBURSEMENT

Reimbursement policies by third parties, like other aspects of therapeutic apheresis, has been the subject of some debate because of the competing factors of cost and therapeutic promise that this case study has variously discussed. The development of most of these policies has been recent, and there would appear to be the groundwork for an even more intensified period of evaluation, debate, and formulation of these policies in the near future. The following review elaborates on these developments and issues.

Federal Policies

The Federal Government has been substantially involved in the funding of apheresis through research support (see ch. 3); benefit programs such as Medicare, Medicaid, military, and Veterans' Administration hospitals; and employee insurance packages such as the Department of Defense's Civilian Health and Medical Program of the Uniformed Services (CHAMPUS) and the Federal Employee Health Benefit Plans.

Medicare*

Although the cost of apheresis has focused attention on reimbursement, cost information has not been explicitly or directly considered in Medicare coverage determinations. The legislatively mandated practice of paying usual and customary fees does not easily accommodate such analyses. Instead, Medicare coverage determinations have relied on safety and efficacy criteria in an effort to "sketch the boundaries of accepted good medical practice" **(98).**

Formal Federal policies for reimbursement of apheresis under its Medicare program have developed almost completely over just the past few years, probably reflecting the fact that HCFA procedures for making coverage decisions were highly informal until early **1980.** The staff of the Office of Coverage Policy, often with assistance from the Health Standards and Quality Bureau, would review the issue, consult experts in the field with whom they were acquainted, and come to a decision **(104). Three or four regional office inquiries concerning coverage positions on apheresis surfaced during that period, but no national instructions were issued.**

Although a formal agreement between HCFA and the Public Health Service had existed since around 1966, a somewhat more formal, systematic, and credible assessment process involving a panel of physicians within HCFA and from NCHCT was established in early **1980.** When

● **On Apr.** *20, 1983,* **Public Law** 98-21 provided for extensive changes in Medicare reim**bursement policies for hospital-based care. Under the statute, whose provisions will be phased** in over 3 years, hospitals will receive a flat fee per patient, set prospectively, on the basis of patient diagnosis in one or more of ***467*** diagnosis-related groups **(DRGs). It is unclear at this point how the DRG-based payment system will affect the adoption and use of apheresis. What is certain,** however, is that information on the effectiveness of this treatment will be even more important as physicians and patients face increasingly scarce resources.

HCFA decided that a procedure involved a question of national importance, a request for a technology assessment was sent to NCHCT. Usually such a request asked NCHCT to determine the safety and efficacy of a particular technology and to recommend whether HCFA should reimburse **(103,104).** Because the number of questions about coverage of apheresis increased substantially beginning in **1979-80 (56),** HCFA, on the advice of NCHCT, issued its first national instructions ***on*** apheresis in August **1981. Effective September 15 of that year, HCFA announced the coverage of therapeutic apheresis for the following indications (52):**

1. plasma exchange for acquired myasthenia gravis;
2. leukapheresis in the treatment of leukemia; and
3. plasmapheresis in the treatment of primary **macroglobulinemia (Waldenstrom) and hyperglobulinemias, including multiple myeloma.**

The HCFA policy statement went on to say that apheresis should be denied for other indications, but that information on claims for what seems to be other nonexperimental uses should be provided to HCFA'S central office **(53).**

Even before the August policy release-in May of 1981—HCFA requested that NCHCT evaluate the safety and clinical effectiveness of apheresis for the treatment of (38):

1. Goodpasture's syndrome;
2. systemic lupus erythematosus;
3. membranous and proliferative glomerulonephritides;
4. multiple sclerosis;
5. potentially life-threatening complications of rheumatic diseases (rheumatoid arthritis, systemic lupus erythematosus, polymyositis/dermatomyositis, and progressive systemic sclerosis); and
6. thrombotic thrombocytopenic purpura (TTP).

NCHCT issued formal assessments on the indications of multiple sclerosis, rheumatoid arthritis, rheumatoid vasculitis, and TTP. Two other indications— Goodpasture's syndrome and membranous proliferative glomerulonephritides-were evaluated in early 1983 by the Center's organizational successor, the Office of Health Technology Assessment (OHTA) (28). (NCHCT and OHTA assessments are discussed in ch. 3.) HCFA has yet to implement instructions on any of these six categories for national coverage policies.

Although Medicare's national coverage is relatively new, it is not unlikely that many hospital apheresis treatments for Medicare patients with covered and noncovered disease indications have been performed and reimbursed without official sanction of HCFA. Because Professional Standards Review Organizations do only a limited job of surveillance, because descriptions in the line item billings are very general, and because new procedures often do not have a procedure code number, the identity of Medicare reimbursements for apheresis therapies may have been concealed (104,117).

Medicare provides coverage for apheresis regardless of whether ***or*** not it is performed at a hospital **(108). It has been reported, however, that independent, freestanding settings are less likely to receive reimbursement at this time, fueling speculation that HCFA hopes to control the use of apheresis by limiting reimbursement to hospital-based therapy (73). There is no known intention by HCFA to implement such a regulation at this time or in the near future.**

Medicaid

Medicaid provides medical assistance to low-income individuals. Treatment costs are shared by the States and the Federal Government, Each participating State must provide certain basic health services, but the States have a great deal of leeway concerning specific coverage (102). Medi-Cal (California Medicaid), for example, will approve payment only for apheresis conducted in the treatment of certain diseases, including myasthenia gravis, lupus, and Goodpasture's syndrome. Treatment of such disorders as rheumatoid arthritis and multiple sclerosis, on the other hand, are at present considered investigational and are thus not covered (108). As of August 1982, Medi-Cal was in the midst of a review of all its apheresis coverage policies, and was ex-

pected to formulate a new policy statement concerning its coverage policies (58).

Veterans' Administration (VA) and Department of Defense (DOD)

The extent of VA and DOD involvement in the use of apheresis is reflected in a hospital and blood bank survey by Scoville Associates (108). That survey revealed that 30 VA and military hospitals performed therapeutic apheresis, on 260 patients, and a total number of 1,350 procedures. No breakdown of usage by disease, or whether use was for clinical or research purposes, is available.

Under DOD's CHAMPUS program, the use of apheresis in the treatment of any condition prior to August 1981 was considered investigational and not a CHAMPUS benefit. Since then, however, the CHAMPUS program has taken the basic Medicare policy and expanded it somewhat. CHAMPUS now extends coverage to use of the procedure as a "last resort treatment of certain medical conditions. " The specified indications are (8):

1. myasthenia gravis during a life-threatening crisis;
2. anti-basement membrane antibody nephritis (i.e., as a result of Goodpasture's syndrome);
3. life-threatening immune complex vasculitis;
4. hyperviscosity of the blood associated with multiple myeloma, Waldenstrom's macroglobulinemia, and hypergammaglobulinemia purpura; and
5. TTP.

Private Sector Policies

Like their Federal counterparts, private insurers historically reimbursed on a routine basis for both apheresis procedures and replacement fluids, but have recently begun to examine apheresis procedures more closely and issue explicit policy statements concerning coverage. In March of **1981, Blue Shield of California approved payment for therapeutic plasma exchange and lymphapheresis** in the treatment of severe cases of rheumatoid arthritis if there are acute life-threatening complications or if conventional drug therapy has failed **(80,117).**

At present coverage under Blue Cross insurance programs varies greatly from State to State. For example, the Southern California, Texas, and South Carolina Blue Cross organizations generally follow the Medicare guidelines and will normally approve payment for apheresis. Illinois Blue Cross indicated that their reimbursement schedule depends on the disease being treated and what other therapies have been tried, but that in general, they will approve most requests. Massachusetts Blue Cross covers apheresis for 14 different disease indications. The Greater New York Blue Cross, on the other hand, does not cover apheresis therapy under any of their plans **(61, 79,108).**

The National Blue Cross/Blue Shield Association issued a policy statement in May 1982 as a guideline to local Blue Cross/Blue Shield plans. That policy recommends coverage—in hospital settings only-of nine disease categories including severe myasthenia gravis and leukemia (34). The National Blue Cross-Blue Shield Association policy does not necessarily mandate acceptance and implementation by individual plans, however, and is subject to a possible future review at an appropriate time (16).

Many private insurance companies, too, including Pacific Mutual and Prudential, provide coverage for apheresis regardless of whether or not it is performed at a hospital. As with Federal policies, uniform private third-party coverage is pivotal to the future development of the procedure, particularly in freestanding and commercial settings. The growth of commercial centers has been slowed in some States by the fact that some insurance organizations do not provide benefit payments for apheresis procedures performed outside the hospital. FDA has yet to establish licensing procedures for apheresis centers, and many private insurers have indicated a reluctance to provide reimbursement for therapy under uncontrolled conditions, which could lead to possible treatment overuse and abuse. There appears to be less overall concern, though, in the case of private payers, about future restrictions on reimbursement for apheresis treatment **(108).**

CONCLUSIONS

Acknowledgment of apheresis as a safe and effective treatment application, as an acute therapy in a small group of relatively uncommon diseases, is reflected in present Medicare reimbursement policy. Suggestive evidence of the safety and efficacy of apheresis in a host of other disorders has also forced a flurry of reimbursement policy reviews and formulations among both government and private party insurers.

Reimbursement policies to the present have revealed an increasingly cautious and explicit approach to coverage of apheresis for almost all disease indications, and understandably so. Apheresis is still not a proven cure for any disorder. It may need to be done repeatedly for certain disease conditions, at a cost of up to $1,200 *or* more each time. Total cost estimates potentially run into the billions of dollars. Nevertheless, by treating certain disease complications, apheresis has reportedly lessened suffering and helped prolong lives. Reliable estimates of these benefits have yet to be determined and quantified. As a result, cost-benefit ratios and CEAS have not yet been conducted.

It should be reemphasized that the formation of cost-benefit ratios and CEAS should not be considered only economic tools. This point is not negated by the fact that CEA/CBA is described as an efficiency-based technique. Measurement of the efficiency of therapeutic apheresis will depend as much on output as on resources used to produce the output. One of the critical output or outcome measures that can be addressed by CEA/CBA is the effect of apheresis on health status or other health outcome related effects. Any CEA/CBA that attempts to analyze such outcomes for an evaluation of therapeutic apheresis will only be as comprehensive and valid as the data on the efficacy and safety of apheresis. Thus, health outcome related CEA/CBAs for apheresis are dependent on the existence of an adequate efficacy and safety information base. The status of such information for many disease indications for which therapeutic apheresis has been used, however, is inadequate. As a result, it may be exceedingly difficult to demonstrate therapeutic apheresis a cost-effective technology for which third-party payment is justified.

Medical insurers are presently far from a consensus on which disease indications should be covered, probably stemming from a less than consistent scrutiny of the evidence on safety and efficacy. A widening of Medicare and private insurer coverage of therapeutic apheresis for specific life-threatening complications (e.g., rheumatoid vasculitis) is probable in the near future. But direct cost estimates and the potential cost of possibly premature diffusion alone make it unlikely and unwise that third-party payers will support any broad extension of benefits for apheresis treatment until more valid data is generated. Until evidence is available, therapeutic apheresis will largely be viewed as an experimental technique, not to be considered as a part of routine care. In light of such a situation, present research and clinical trials being carried out assume even greater importance. It will be several years, though, before all the results are in.

Lastly, a significant (but still speculative) factor amidst the cost and reimbursement policy debate is the potential cost reductions of new apheresis equipment and treatment modalities. The present trend towards plasma perfusion (more selective removal of undesirable plasma fractions) offers the possibility of eliminating the need for replacement fluids which could reduce the present cost per treatment by *20* to *50* percent. Staffing charges are presently based on a large proportion of acute treatments which are usually performed on an in-patient basis, often at the patient's bedside. Some observers predict the future growth in apheresis to involve increases in maintenance therapies which could be performed on an outpatient basis, with reduced involvement of hospital staff **(74,108).**

On the other hand, there seems to be a trend toward in-hospital use in areas such as Washington, D.C. **In that region, after the Red *Cross*** started doing therapeutic apheresis in March **1978, only one of the first 16 months' 106 procedures was done in a hospital. But from July 1980 to**

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April 1981, nearly five out of six were. Future decisions regarding treatment settings will no doubt depend on a number of factors such as hospital charges, regulation and standard setting activities for freestanding, independent commercial clinics, reimbursement policies, and whether apheresis is administered largely for reasons of acute or maintenance therapy in specific disorders.

5 .
Implications for Policy

5. Implications for Policy

In summary, the confluence of technological advances in apheresis equipment and recent scientific research linking many chronic disease conditions to immunological dysfunction has served to expand dramatically the number of apheresis procedures in the pasts to 10 years. Therapeutic apheresis has exhibited many of the classic features that have come to characterize the hopes, concerns, and fears about medical technologies over the last three decades.

Utilization and diffusion of therapeutic apheresis seems to have closely followed Warner's (141) "desperation-reaction" model. Initial rapid diffusion has occurred in the absence of safety and efficacy evidence. The rapid diffusion is due in part to a lack of a suitable alternative technology, in part to claims—some of them dramatic—of the technology's beneficial effects, and in part to desperation on the part of patients and of providers responsible for treatment. In chronic and life-threatening situations, apheresis has found its broadest and most frequent application.

Most recently, however, the lack of well-validated clinical evidence has influenced provider behavior. Ambiguous results have given rise to physician caution, while lack of evidence and high costs have provoked increased regulation by medical insurers, possibly slowing diffusion. Best estimates are that utilization and diffusion have plateaued, at least for the present. The future of therapeutic apheresis seems predictable in that increases or declines in use will be predicated on newly available evidence (35,95).

Several recurring issues in need of further study and resolution have run through the examination of therapeutic apheresis. One issue, given the current state of this technology and many unanswered questions about patient criteria for use, **is** what constitutes the appropriate timing of intervention in the course of a disease and whether the procedure to be followed in performing therapeutic apheresis is adequately standardized. Such questions are basic in the development of the technology, and research to address them is necessary, as it forms a foundation for the conduct of well-controlled testing and clinical trials. The Apheresis Panel of the American Medical Association's Council of Medical and Scientific Affairs has recently discussed the idea of a national apheresis registry that would track use and form a knowledge base for development of well-controlled studies **(32).** On a smaller scale, the American Red Cross has requested its regional blood services to register all apheresis patients at the onset of treatment and report treatment methods and results upon completion (1.21).

A second issue, which arises where conditions of use have been sufficiently standardized, is the lack of well-designed research studies and the need for such undertakings. There have been at least two obstacles preventing the accumulation of valid evidence of safety and efficacy: the ethics of providing sham apheresis or conventional therapy for control group patients, and the high costs of such trials. Long hours of sham apheresis procedures, while possibly inflicting on control group patients some of the same side effects of apheresis as treatment group patients, has led to questions of the ethical implications of such trials. Furthermore, in life-threatening or severely debilitating situations, doctors feel they cannot ethically deny apheresis therapy to control group patients.

The obstacle of costs of well-designed studies has been partially offset by a recent infusion of Government and foundation funding. Should costs continue to be a problem, one alternative might be to have third-party payers, including Medicare, selectively reimburse for therapeutic apheresis in return for clinical data. If implemented properly, this alternative could substantially increase the quality of information available for public and private reimbursement coverage decisions. Evidence of the technology's cost effectiveness could result in yielding substantial budgetary savings. Even if the results of such trials were disappointing, they could lead the way to unexpected advances in research (47).

Because of the promise of apheresis for certain disease complications, this technology would appear to be a particularly choice candidate for such a policy course. In such conditions as Goodpasture's syndrome, for example, effective alternative therapies are very limited and the disease is frequently fatal. Because apheresis has been claimed effective, selective reimbursement could be of great utility from both research and clinical standpoints.

There would be problems in implementing this alternative (see e.g., 104), primarily concerning the legal and ethical implications of selectively reimbursing for health care. It seems clear, however, that third-party payers could use this approach to encourage less costly and more effective forms of treatment. In the case of Medicare, too, elements of the Public Health Service could be involved in developing research protocols and in interpreting research evidence from the resulting experiments.

A recent precedent exists for third-party payer participation in clinical trial funding for apheresis. Five Midwestern State or local Blue Goss/Blue Shield groups and other third-party payers have agreed to reimburse five centers involved in a randomized clinical trial of apheresis for multiple sclerosis. Both the investigational procedure and a sham procedure are covered. Medicare and the State Medicaid groups, on the other hand, **are not** participating, but administrative and other research costs of the trial are being funded through a National Institutes of Health grant **(97).**

The Arthritis Foundation and the National Multiple Sclerosis Society are also sponsoring a meeting (to be held in July 1983) at which they hope to develop proposals for third-party payer participation in funding other clinical trials. Representatives of both private and public insurers will be participating (97).

A ***third*** issue is the possibly transitional nature of this technology. Some major new hardware developments are now undergoing clinical tests. These use adsorption columns and membranes that work like molecular sieves. When a specific fraction whose removal is desired can be identifed, an adsorption column containing an antibody to that fraction can remove it from the plasma as **it** passes through. Another method, resembling hemodialysis, passes the blood across a membrane with a specific antibody attached to it. A third technique uses a membrane filter to remove fractions of a specific molecular weight **(80).**

These advances in equipment may, in the course of the next decade, be reinforced or even overshadowed by advances in basic biomedical research or in emerging parallel developments such as biotechnology. The National Cancer Institute, and the National Heart, Lung, and Blood Institute, for example, are currently supporting strategies for the separation of complex blood proteins. Advanced separation technologies could make it possible to index most human proteins. Once proteins **are** displayed and distinguished from one another, investigators might then tease out individual functions and relate them to the DNA code. Other activities could include the detection of abnormal protein patterns in disease states (e.g., leukemia), and the corresponding production of preventive or neutralizing elements (e.g., monoclinal antibodies) to these noxious or damaging processes **(53,60).**

In the final analysis, such a state of scientific and technological flux has important policy implications. Therapeutic apheresis, as a medical intervention, falls into a category of medical technologies classically referred to as half-way ***technologies*** (133). These are generally treatments directed at correcting the effects of a disease or palliating them. It has been pointed out and illustrated repeatedly in the literature and research community that such measures are less satisfactory and more costly than so-called ***definitive technologies,*** which effectively prevent or control a disease or condition (e.g., poliomyelitis vaccine). As Robbins **(116)** and numerous others have asserted, "where alternatives exist, resources should be directed so as to encourage the development of definitive technologies as opposed to half-way measures." To the extent that such alternatives can be identified, considerable attention should be given to the possibility of devoting resources to their development. Indeed, one of the critical, ongoing policy issues in medicine is how to establish the most rational and productive balance between development and support of half-way technologies and that of basic research toward definitive technologies.

Appendixes

Appendix A.— Health Program Advisory Committee and Acknowledgments

HEALTH PROGRAM ADVISORY COMMITTEE

Sidney S. Lee, *Chair*
Michael Reese Hospital and Medical Center

Stuart H. Altman*
Florence Heller School
Brandeis University

Carroll L. Estes
Department of Social and Behavioral Sciences
School of Nursing
University of California, San Francisco

Rashi Fein
Department of Social Medicine and Health Policy
Harvard Medical School

Melvin A. Glasser
Health Security Action Council-
Committee for National Health Insurance

Patricia King
Georgetown Law Center

Joyce C. Lashof
School of Public Health
University of California, Berkeley

Margaret Mahoney
The Commonwealth Fund

Frederick Mosteller
Department of Health Policy and Management
School of Public Health
Harvard University

Mitchell Rabkin*
Beth Israel Hospital
Boston, Mass.

Dorothy P. Rice
Department of Social and Behavioral Sciences
School of Nursing
University of California, San Francisco

Richard K. Riegelman
George Washington University
School of Medicine

Walter L. Robb
Medical Systems Operations
General Electric
Milwaukee, Wis.

Frederick C. Robbins
Institute of Medicine

Rosemary Stevens
Department of History and Sociology Science
University of Pennsylvania

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Appendix B.—Apheresis for Hemolytic-Uremic Syndrome

Prepared for OTA by: Paul M. Wortman, Ph. D.
Hillary Murt, M.H.S.A.
In collaboration with: Bruce Friedman, M.D.

The most prominent feature of hemolytic-uremic syndrome (HUS) is renal microangiopathy, which is characterized by endothelial damage in glomerular capillaries and renal arterioles. The event which initiates this endothelial damage is unknown although some authors have suggested that endotoxin is a prime candidate (71). The damaged endothelial cells become swollen, leading to renal ischemia and decay of kidney function and two secondary hematologic events—red cell destruction (hemolytic anemia) and a dramatically reduced level of circulating platelets (thrombocytopenia). The former results from mechanical damage to red cells passing through the damaged vessels. The reduced platelet count results not only from trauma but also localized intravascular coagulation (and platelet consumption) occurring in the damaged vessels.

An alternative and more recent hypothesis cites decreased formation of PGI_2, (prostacyclin) as the precipitating event leading to the full-blown clinical manifestation of the syndrome (instead of a toxic agent such as endotoxin). The finding of $PG1_2$ deficiency in adults and children with HUS supports this concept (11). In this case, the loss of PGI_2, causes localized platelet aggregation in renal vessels and vascular obstruction. Traumatic red cell destruction (hemolytic anemia) is a corollary of the development of the microthrombi which partly occlude the vascular lumens (84).

Finally, Seger, et al. (126), have suggested that HUS is a polyetiologic syndrome with neuraminidase being the culprit agent in some cases, particularly among children suspected of having pneumococcal infections, as this agent can produce lesions in all three cell systems (red blood cells, platelets, and endothelial cells).

The hemolytic-uremic syndrome shares a number of features, including vascular endothelial damage, with thrombotic thrombocytopenic purpura (TTP). In fact, HUS has been considered by some clinicians to be a variant of TTP, this being supported by similar 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). These authors believe, however, that a clinical diagnosis of one or the other conditions must be made because the treatment differs and in HUS, depends on the management of the complications associated with renal failure.**

Plasma exchange (PE) was first administered as a therapy for TTP in 1959 by Rubenstein and others (84). Rapid and sustained recovery was observed after two exchange transfusions with fresh whole blood to an n-year-old patient.

Taft and Baldwin (132) noted that centers which have experience with five or more patients diagnosed with TTP and treated with PE are reporting survival rates in the 60- to 80-percent range. Plasma exchange is now being advocated as a potential therapy for treating HUS because of the suspected etiological similarity between the syndrome and TTP. Apheresis is viewed as being potentially helpful in removing a toxic agent (e.g., endotoxin, neuraminidase) or replacing a missing factor, possibly a physiological inhibitor of platelet aggregation. In the latter case, Beattie, et al. (11), and Misiani, et al. (84), have both suggested that PE using normal plasma replaces a missing factor needed for stimulating PGI_2 production by vascular endothelium.

Specification of Treatment

Only eight reports (including two letters to the editor and one abstract) have been published in the English medical literature on the effectiveness of plasma exchange in the management of HUS. These eight communications account for 11 patients diagnosed with HUS ranging in ages from 1½ to 59 years who were treated as an ancillary therapy with corticosteroids, antiplatelet drugs, or heparin. * Moreover, in seven

● Beattie, et al. (11), report on a 3%-year-old boy diagnosed with HUS. The patient was initially treated with aspinn and dipyrimadale (s mg/kg/day) and his condition gradually improved. Plasma exchange was not initiated until 10 days later when the patient was readmitted to the hospital with recurrent symptoms of HUS. The authors do not indicate whether any drug therapy was administered during the second episode, so it is assumed that PE was the only therapy administered. The article by Taft and Baldwin (132) focuses primarily on the treatment of patients diagnosed with TTP. They only briefly mentioned two patients with HUS who were treated with apheresis and do not provide full case histories.

cases hemodialysis or peritoneal dialysis was performed concurrently with plasma exchange.

It appears that apheresis is not the sole treatment regimen of HUS and thus the particular impact on patient health may be hard to determine. Apheresis is commonly embedded within a more comprehensive treatment regimen including a variety of drugs, some form of dialysis, and blood or platelet transfusions. Several authors (84,132) have mentioned the difficulty in evaluating the efficacy of each treatment approach alone since different forms of therapy have typically been employed in combination. Misiani, et al. (84), for example, are concerned with separating the beneficial effects of PE from antihypertensive drugs in treating HUS, whereas Taft and Baldwin (132) emphasize the need to evaluate the relative contributions of ancillary therapies such as corticosteroids and antiplatelet drugs to the successful recovery of PE-treated patients.

Despite the fact that a sizable proportion of HUS patients are treated with some form of dialysis, none of the authors point out the possible confounding effects of hemodialysis and peritoneal dialysis performed concurrently with plasma exchange. It should be noted that dialysis may provide beneficial effects independent of apheresis. In the case of hemodialysis, all patients are heparinized during dialysis. Heparin, an anticoagulant drug, exerts an antithrombotic effect. Recall that thrombotic occlusions of capillaries and arterioles have been implicated in the pathogenesis of HUS. Thus, hemodialysis (which necessarily includes the administration of heparin) may be partly responsible for inhibiting the formation of microthrombi in the glomerular capillaries and thereby increasing renal blood flow.

Heparin was also administered to one HUS patient in the absence of hemodialysis, which suggests that clinicians recognize the potential efficacy of using heparin therapy alone for treating HUS. Parnes, et al. (106), report on two small series of HUS patients treated with only heparin; mortality rates of 9 and 50 percent were recorded. In each series, about 30 percent of the patients completely recovered; the remaining underwent chronic dialysis.

In the case of either hemodialysis or peritoneal dialysis, it may also be postulated that the removal of unspecified substances of low molecular weight may ameliorate the symptoms of HUS, if the substances that are removed are responsible for the development of the vascular lesions.

It is important to draw 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. Although the plasma replacement in early cases was initiated only for purposes of expansion of the intravascular volume, later authors suggested that the administration of fresh frozen plasma had an independent therapeutic effect. This led some investigators to administer it alone with apheresis; this is described in the literature as plasma infusion. The beneficial effects of PE may be confounded when plasma infusion is also administered as part of the treatment regimen. Obviously, both methods have the advantage of replacing the missing plasma factor, if, in fact, that is the underlying cause of HUS. However, PE may provide the additional advantage of removing other possible etiological agents, the products of damaged red blood cells, and other hypothetical platelet aggregating substances. In short, when these two forms of therapies are both administered during a relatively short period of time as in the case of two HUS patients described in the literature (84) it becomes difficult, if not impossible, to attribute any measure of success to one therapy or the other.

It is conceivable that some form of adjuvant drug therapy or dialysis is required in conjunction with apheresis to successfully treat patients with HUS. That is to say, clinicians may view PE as a necessary but not sufficient form of treatment to restore normal physiological functions. When other forms of therapy are used in addition to PE, particularly drug therapy, there still is the problem of operationalizing the treatment when the concomitant therapies vary widely across cases (e.g., the use of heparin with or without platelet inhibitors). When there is differential improvement by type of drug used, the integrity of the treatment is called into question. It may be the case that the synergistic effects of apheresis and drug therapy may vary according to the dosage and regimen of the particular drug used.

Plasma exchange therapy itself varies widely with respect to the number of exchanges performed and the volume of plasma removed at each exchange process. Table B-1 shows that the number of PEs performed for each episode of HUS ranges from one to eight exchanges for the 11 patients diagnosed with HUS. In two of the studies, the frequency of plasma exchange appears to be dictated by the platelet response (spontaneous increment v. lack of increment), and the level of serum LDH activity or creatinine levels. In one study, however, the frequency of plasma exchange in another study depended on the resolution of neurologic symptoms *(sO).* As best as can be determined from table B-1, the volume of plasma removed at each exchange is variable. However, the discrepancy in the volume of plasma removed at each exchange across patients may be due to the fact that 7 of the 11 pa-

Table B-1.—Apheresis Experience Among Patients Diagnosed With Hemolytic-Uremic Syndrome

Study reference number	Number of patients	Age range of patients	Range of plasma exchanges performed per episode	Range of plasma volume removed per exchange	Types of replacement fluids used
	1	3½ yrs.	2	1,000 ml	Fresh frozen plasma
1	2	7 yrs.	3	Unknown	Whole blood
5	2	54-56 yrs.	1	3,000 ml	Fresh frozen plasma
6	1	21 yrs.	5	3,000 ml	Fresh frozen plasma and normal saline
7	2	19-22 mo.		1,500 ml-2,350 ml	Whole blood
8	1	8 yrs.	8	1,500 ml	Albumin, fresh frozen plasma
9	2	2-7 yrs.	1-6	27 ml/kg-89 ml/kg	Whole blood, fresh frozen plasma
10	1	37 yrs.	4	Unknown	Unknown

SOURCE: Office of Technology Assessment, 1983.

tients undergoing PE were children, who have smaller blood volumes. Table B-1 also shows that whole blood and fresh frozen plasma are the two most common replacement fluids used in the process of plasma exchange for patients with HUS. Human serum albumin was used as a replacement fluid in only one case and the authors noted that there was no improvement after three exchanges, suggesting that no circulating agent perpetuated the condition. Plasma exchange was then performed with fresh frozen plasma, which was followed by a prompt recovery in the platelet count (131).

The absence of explicit and detailed protocols for performing plasma exchange poses a major problem in the evaluation of the effectiveness of apheresis therapy. However, given the rare occurrence of HUS in the population, it comes as no surprise that not enough information has been accumulated on the use of plasma exchange to develop such protocols.

Misiani, et al. (84), suggest that at the present time it is impossible to define individual PE requirements since both the patient's and donor's plasma may differ with respect to the plasma factor (e.g., PGI_2) concentrations. Those authors recommend apheresing a full volume at the initial exchange, followed by one-half the initial amount daily until full hematologic remission is obtained. The literature on TTP, on the other hand, is considerably more extensive and consequently, a set of treatment guidelines or protocols has recently been proposed by Taft and Baldwin (132). They have developed a clinical scoring system (including necrologic evaluation) to evaluate the day-to-day severity of the disease, which maybe used to determine the frequency of PE. Relying on five clinical criteria (i.e., platelet count, serum LDH, total bilirubin, creatinine, and necrologic status) a score is calculated to determine whether therapy should be continued. Since several investigators have suggested that HUS is a variant of TTP, it is conceivable that such a scoring system modified slightly to take account of the clinical manifestations specific to HUS could be used to determine the appropriate frequency and volume of PE.

Outcome Measures

A recurring critical issue in any attempt to analyze the effectiveness of a medical innovation is the selecting of appropriate endpoints for evaluating the success or failure of the innovation. In many instances, outcome measures are either lacking, not specified, or ill-defined in the written reports. For example, one study of HUS reports that the patient "showed improvement" after the PE was initiated, without defining precisely what improvement means (135).

It appears that on, the whole, nonspecification of outcome measures is less of a problem when evaluating the effectiveness of plasma exchange for patients with HUS. While it is noteworthy that none of the eight studies provide a discussion that specifically focuses on the kinds of outcome measures that should be used to evaluate apheresis for HUS, there does appear to be some consensus in the literature on the array of clinical indicators that are reported pre- and post-PE.

Table B-2 shows, for example, that all eight studies reported whether or not their patients underwent chronic dialysis and their mortality experience. However, the length of followup during which mortality data were collected varies across studies, which may limit the usefulness of directly comparing mortality rates, Furthermore, seven of the eight studies reported creatinine or BUN levels (i.e., indicators of renal insufficiency) and six studies indicated platelet counts. All six indicators displayed in table B-2 should be *con*sidered to be objective outcome measures. That is to say, none of these measures is likely to be influenced

Table B-2.—Variability in Effectiveness of Plasma Exchange Therapy for Hemolytic-Uremic Syndrome as Expressed in Selected Outcome Measures (all outcome measures relate to past plasma exchange period)

Study reference number	Number of patients	Outcome measures: Patients with increment in platelet count	Patients with eventual decline in serum LDH	Patients with remission of neurologic signs	Patients with eventual decline serum creatinine or BUN (renal improvement)	Patients for whom chronic dialysis was initiated or continued	Mortality
1	1	1/1	NA	NA	**0/1**	1/1	**0/1**
2	1	NA	NA	1/1	**1/1**	**0/1**	**0/1**
5	2	2/2	2/2	NA	**1/2**	**1/2**	**1/2**
6	1	1/1	NA	NA	**1/1**	**0/1**	**0/1**
7	2	NA	NA	NA	0/2	2/2	2/2
8	1	1/1	NA	NA	1/1	0/1	**0/1**
9	2	212	2/2	NA	212	0/2	0/2
10	1	1/1	NA	NA	1/1	0/1	0/0

NA-Not available.

SOURCE: Office of Technology Assessment, 1983.

by expectations of the physician or patient concerning the efficacy of treating HUS with apheresis.

These measures clearly represent endpoints that are evaluated at different times during a given episode of HUS. It may, in fact, be convenient to make a distinction between the more general measures of health status relating to HUS (e.g., chronic dialysis, mortality), which represent the sum total of many influences and the more sensitive and specific hematologic, biochemical, and clinical signs and symptoms (e.g., platelet count, creatinine, BUN, serum LDH levels, and neurological status) that often occur rapidly following plasma **exchange. The former may be called 'long-term" outcomes, whereas the latter may be termed "immediate" outcomes.**

When an outcome measure such as mortality is used to evaluate the effectiveness of apheresis therapy for HUS, 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, may be a more appropriate outcome measure for determining the ultimate success of plasma exchange in the treatment of HUS, since renal failure is a major element of the syndrome. Chronic dialysis was deemed necessary for 4 of the 11 patients listed in table B-2 (two of whom later died) which represents a 36-percent failure rate when dialysis is used as the sole measure of the effectiveness of PE therapy.

Finally, changes in hematologic and biochemical parameters such as platelet count, serum LDH, creatinine, and BUN levels may also be used to evaluate the effectiveness of apheresis therapy. The difficulty with using these measures, however, is that patients may show improvement in one or all of those parameters yet still require long-term dialysis (e.g., patients in studies 1 and 5). In short, the "immediate" outcome measures may be necessary but insufficient indicators of the efficacy of plasma exchange. Perhaps these measures and the end points of chronic dialysis and mortality could be combined in some way as co-measures. 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 PE in treating HUS.

Patient Selection

In seven of the eight studies, PE therapy was initiated when patients diagnosed with HUS did not respond to either hemodialysis or peritoneal dialysis or other conventional therapies including corticosteroids, antiplatelet drugs, or heparin. In other words, apheresis was performed on these patients as a last resort therapy when there were no other effective alternative therapies and death was the likely outcome. Since only the "worst cases" of HUS appear to be selected for apheresis therapy, it is possible that the effectiveness of plasma therapy is underestimated, depending on which outcome measure is used. If PE is initiated in the later stages of the disease (i.e., when end-stage renal disease is inevitable), the beneficial effects of

apheresis maybe dramatically reduced if chronic dialysis is the end point used for evaluating the effectiveness of the treatment.

Evaluation of the Evidence

The eight communications that have appeared in the literature during the past 3 years describing the effectiveness of apheresis in treating patients with HUS present data on a total of 11 patients, but each case is described individually. Only one of the communications suggests that PE has limited effectiveness on the disease process (11). However, the authors in this article add that the clinical benefit may have been compromised because PE 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 PE be initiated during the early stages of the disease in order to realize its full benefit (132). Parries, et al. (106), caution that PE alone is associated with complications (e.g., hepatitis) and that these risks should be weighed against the potential benefits of apheresis.

What can be said about the "scientific soundness" of the data on which the conclusion that PE is efficacious is based? Scientific soundness is defined here as the adequacy and the credibility of the available information for reaching a consensus. First, in the case of evaluating the use of PE therapy for treating HUS, it is quite clear that the newness of this particular application of the technique is associated with a small and incomplete research base. With only 11 patients, there is insufficient data on which to make a recommendation to endorse this procedure. Second, the credibility of the evidence is open to question because of the quality of research used in all eight studies; these case studies do not include any comparison groups. The major problem with the case-study approach (and other pretrial studies) is that they are subject to a variety of competing alternative explanations for the observed effects of the therapy. Interpreting the evidence becomes even more problematic when the potential affects of apheresis therapy are confounded by other therapies that are used concomitantly with plasma exchange. Apheresis was the single therapy used in only two case studies; one patient completely recovered and the other patient underwent chronic dialysis because of continued deterioration of renal function (11,106).

Finally, it is unclear as to which criteria (e.g., outcome measures) should be used in evaluating the effectiveness of the therapy. There are too few cases to determine whether there is high concordance between the "immediate" outcomes (e.g., platelet counts, LDH, creatinine, and BUN levels) and the "long-term" outcomes (e.g., chronic dialysis, mortality). If these measures turn out to be discordant, some method will have to be developed to combine these multiple evaluative criteria in order to arrive at the recommendation.

Appendix C.—Apheresis for Inhibitors to Factor VIII

Prepared for OTA by: Paul M. Wortman, Ph. D.
Hillary Murt, M.H.S.A.
In collaboration with: Bruce Friedman, M.D.

Factor VIII Antibodies

Apheresis, and more specifically, plasma exchange (PE), has been investigated as a potential therapy for patients with antibodies or inhibitors to Factor VIII during the past 10 years. Factor VIII is essential to achieve hemostasis (i.e., permit normal blood clotting and end bleeding). For that reason, patients with classic hemophilia have been particularly at risk from complications associated with the development of Factor VIII antibodies. 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 childbirth, persons with rheumatoid arthritis, the elderly, and persons suffering a variety of other disorders.

The major concern in these situations has been to return Factor VIII to normal or effective levels. Treatment typically involved immediate and continued doses of human Factor VIII concentrate. This treatment often failed since it did not remove existing antibodies in the blood and frequently appeared to stimulate the production of more antibodies. To deal with these complications a variety of alternative treatments has been investigated. One of these has involved the use of apheresis with or without Factor VIII. The following sections summarize the available scientific research reporting on the use of PE in treating patients with antibodies to Factor VIII.

Literature Reviews

Twenty articles were located and retrieved from a MEDLARS search of the research literature. Four of these articles did not deal specifically with cases involving Factor VIII, five were in a foreign language (two in Russian, two in German, and one in Hungarian), one article was a duplicate copy of another, and one contained the same case information as another by the same authors. Of the foreign language articles, the two in Russian were excluded, the one in Hungarian also was published in English and that article was included in our review; the two German studies were read. One of the German articles did not deal with Factor VIII and the other presented a very brief case drawn from 210 patients and also was not included in this review.

There remained nine articles to review after the various exclusions were made. The articles were all case studies involving from one to six patients. Five studies reported treating a single patient; two had two patients; one had three, and another had six. Of the 18 patients in these nine studies, 10 had classic hemophilia, seven idiopathic Factor VIII antibodies, and one had von Willebrand's disease. The patients generally faced a life-threatening situation. Thirteen had severe bleeding and three required or were recovering from surgery. The patients ranged in age from 3 to 77 and generally had either low levels of Factor VIII or high levels of Factor VIII inhibitor reported prior to treatment.

Table C-1.—Apheresis Experience Among Patients Diagnosed With Inhibitor to Factor VIII

Study reference number	Number of patients	Range of PEs per episode	Range of plasma volume removed per exchange (in ml)	Replacement fluids used	Duration (days)
1	1	9	500-1,500	FFP[a], saline	42
2	1	2	3,800-7,500	FFP	21
3	2	6-8	1,500-3,000	FFP, albumin	8-10
4	3	1-2	1,500-3,000	Gelatin, albumin, saline	2-50
5	1	3	17,100 total	FFP	1
6	1	3	1,400-6,000	FFP	7
7	1	3	600-1,000	FFP	18
8	2	3-15	4,000	FFP, saline	3-14
9	6	1-4	2,500-3,500	Gelatin, plasma protein	1-4

[a]FFP = Fresh, frozen plasma.

SOURCE: Office of Technology Assessment, 1983.

Specification of Treatment

Although apheresis was employed in all of these studies, the actual definition or specification of treatment varies widely from one report to another (see table C-1). First, the number of PEs vanes widely from just 1 (109,143) to 15 (129). The modal number of PEs was three (occurring in six of the *18* patients) with another four receiving two exchanges. The volume of plasma actually exchanged also differed widely from one study to the next, ranging from 500 to 6,000 ml per exchange. The replacement fluid also varied. Although in seven studies fresh frozen plasma was used, other fluids included albumin, gelatin, plasma protein, and saline (or plasma expander). It should be noted that in most patients who were severely compromised fresh frozen plasma was used. The treatment also varied in duration, lasting from 1 day to *6* weeks.

Perhaps most troublesome in determining the appropriate treatment regimen is the use of immunosuppressants such as azathioprine and cyclophosphamide in conjunction with apheresis. Five of the eight studies used one of them simultaneously with PE and two had tried it before using PE. Nevertheless, there is a great difference of opinion on the value of such therapy despite its confounding with apheresis. One study (129) claims that "immunosuppression has not been shown to be effective and may well interfere with wound healing and increase susceptibility to infection." However, another study (111) concludes that "a combination of specific immune suppression and intensive . . . (apheresis) . . . may be the best form of treatment in patients with acquired idiopathic factor VIII inhibitors and life-threatening bleeding." The resolution of these conflicting claims and the separation of the two treatments (PE and immunosuppression) poses some difficulties in so few studies.

The study by Pintado, et al. (111), contains the best discussion of possible alternative treatments. In that study one elderly patient with idiopathic or acquired Factor VIII inhibitor was given six plasma exchanges over a 2-week period. These researchers reviewed the previous literature and concluded that "spontaneous remission of the immune response" (i.e., termination of production of Factor VIII antibodies) was "unlikely." Instead, they feel that the remission was due to the combined use of immunosuppressants and "antigenic load" (i.e., human Factor VIII concentrate).

Treatment with Factor VIII concentrate poses an additional problem in determining the efficacy of apheresis. As noted in the introduction, Factor VIII supplementation is viewed as the primary treatment with apheresis an adjunct to improve its efficiency. The use of Factor VIII was, in fact, reported in all nine studies encompassing 16 of the 18 patients treated. However, in one study (37) involving two patients, this treatment was evidently discontinued just prior to apheresis because of a rise in inhibitor level in one patient and an adverse reaction (to a porcine derivative) in the other. Similarly, in the study by Piller, et al. (109), one of three patients was treated with Factor VIII concentrate just prior to apheresis. While the inhibitor level was reduced from 1.3 to 0.5, p/ml, the goal of this study was its complete neutralization and an increase in Factor VIII. In the remaining two patients (who were not in a life-threatening situation) apheresis using Factor VIII-free solutions was tried in an attempt to prevent the "rapid increase" in inhibitor activity. In both cases there was a "less rapid" return of inhibitor activity to its previous level (and, in one case, a "considerably higher" level). The authors conclude that inhibitor levels can be lowered through "repeated . . . (apheresis) . . . at intervals of about one month."

The Piller, et al. (109), study did not employ immunosuppressants concurrently in conjunction with apheresis (although one patient received prior treatment with azathioprine and Factor VIII with cyclophosphamide "without success"). If the hypothesis of Pintado, et al. (111), is correct, then antibodies would continue to be produced requiring regular PE. As noted

Table C-2.—Effectiveness of Apheresis for Factor VIII Inhibitors

	Immediate		Followup
Study reference number	Hemostasis	Factor VIII inhibitor *(μ/ml)*	Factor VIII inhibitor *(μ/ml)*
1	—	1.2	0.8
2	yes	36	8
3	yes	1-8	0-1
4	—	O-4.8	0-17
5	yes	—	0
6	yes	—	0
7	yes	12	0
8	yes	—	
9	yes	0-1	5-47

SOURCE: Office of Technology Assessment, 1983.

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this is exactly the conclusion of Piller, et al. (109). Moreover, the two studies with the greatest number of PEs did not use immunosuppressants. In the study by Slocombe, et al. (129), noted above, one of the two patients received 15 PEs exchanges along with varying doses of Factor VIII. Similarly, Cobcroft, et al. (23), performed nine apheresis treatments on a patient (who had previously had unsuccessful immunotherapy). One can only speculate on whether as many exchanges would have been required had immunosuppressants been employed concurrently. In both studies, however, there is little justification provided for additional exchanges beyond the first two.

In summary, the modal regimen in the research studies involved two or three apheresis treatments in conjunction with both immunosuppressants (typically cyclophosphamide) and Factor VIII concentrate (from humans). Two hypotheses seem tenable from these studies. First, immunosuppressants may stop the production of antibodies as Pintado, et al. (111), claim, with the apheresis quickly removing existing antibodies. And second, apheresis using Factor VIII-free solutions such as gelatin or saline may slow the return of the inhibitor activity as Piller, et al. (109), maintain. The two treatment therapies are clearly not independent and could be combined. At present there is a need for more systematic research on the most appropriate treatment for patients presenting with Factor VIII antibodies.

Results of Treatment

The results of the treatment just described in the nine studies reviewed are presented in table C-2. Both short-term or immediate results and long-term findings are indicated. For 16 of the 18 patients at risk due to severe bleeding or surgery the immediate clinical results were uniformly successful. In all cases hemostasis was achieved and the patient fully recovered from the acute episode. One should note, of course, that cases of clinical failures are much less likely to be submitted or accepted for publication.

The measures of Factor VIII inhibitor (in ~/ml) and Factor VIII (in percent normal) are not consistently reported in the text. Where possible this information was recorded or interpolated from tables and figures. These figures indicate a less than consistent pattern of results. In almost half the patients (i.e., 8 of 18) the inhibitor level falls below 2 @ml at followup; while in 9 of the patients reported, the inhibitor level is 8 µ/ml or greater. The inhibitor data for one patient (129) were not available, but were probably very low given the Factor VIII level of 75 percent.

Eight of the nine patients with poor long-term results are from just two studies (109,143). The Piller, et al., study differed from all the others in that its sole objective, as noted earlier, was the long-term reduction in the Factor VIII inhibitor level. This study did not employ Factor VIII therapy along with immunosuppressants in the two failed cases (although one had received them earlier). It should be noted that short-term control was achieved and the authors conclude that one could "treat severe hemorrhages immediately by only administering Factor VIII or by combining one . . . (apheresis) . . . run with replacement therapy."

The other six patients, one-third of the total from all of the studies, with poor long-term or "secondary rise" in the inhibitor level, were treated by Wensley, et al. (143). In this case, apheresis combined with human Factor VIII concentrate produced an initial lowering of the inhibitor level to permit hemostasis and healing. The authors recommend this combined therapy as a better alternative to using "significant quantities" of Factor VIII alone.

As noted in the previous section, the impact of immunosuppressants should be considered. Neither of these two studies reported the concurrent administration of immunosuppressants to patients. On the other hand, five of the six patients treated with immunosuppressants had followup inhibitor levels of 1 @ml or less.

Evaluation of the Evidence

In conclusion, it is important to ask what one can infer from these nine studies. To do this, it is useful to consider the quality of the research evidence provided. A number of points should be considered in reaching an overall assessment.

First, the studies are all pretrial clinical reports generally of one patient (i.e., the five articles). There were no clinical trials comparing a number of patients systematically treated by a number of well-defined therapies. In fact, other than references to some prior treatment regimen there is no comparative information available.

Second, as an earlier section noted, there is no agreed upon treatment for patients with inhibitors to Factor VIII. While apheresis is used and endorsed in all nine studies, the treatment is more complex than that. Other concurrent therapies are described with varying results and the number of PEs also differed from study to study. While a number of possible hypotheses were examined, the evidence is far from con-

elusive on what is the best method to treat this condition.

Third, the goals of the studies also differed. Most involved acute, life-threatening situations, usually episodes of severe bleeding. In those cases, short-term resolution of the problem was sought and generally achieved. In a few other studies, longer term solutions to the anti-Factor VIII were attempted with varying results. Here too, there are possible treatment combinations that need to be further investigated.

Finally, with so few patients in so few studies one must consider the issue of sample bias. It would only take a few reports of a few patients with differing or negative results to alter one's notion of the efficacy of apheresis in this situation. For this reason the evidence can only be viewed as preliminary and provocative. It is far from persuasive.

Apheresis in combination with other therapy is only an emerging technology for treating patients with Factor VIII antibodies. There is a need for more careful study and specification of the treatment and its effects—both of immediate and longer duration. There are a number of questions that need to be answered before its efficacy is established. If, as is likely, apheresis continues to be employed in life-threatening situations, then physicians should be encouraged to undertake more systematic study of the treatment. This could include a number of therapeutic alternatives systematically applied to a series of patients, perhaps in a controlled trial.

In conclusion, it should be noted that some experts believe all the treatment combinations described above are not effective. In particular, PE is viewed as a stopgap measure, at best, because (as the literature indicates) the antibody titer rapidly increases post exchange. For these reasons current interest has focused on bypassing the blockade of the Factor VIII inhibitor by administering new agents that contain a mixture of clotting factors, including activated Factor VIII. Given the availability of these new agents, such treatment may be the therapy of choice for patients with high titers of Factor VIII antibodies.

Appendix D.—Apheresis in Guillain-Barre Syndrome

Prepared for OTA by: Richard K. Riegelman, M. D., Ph. D.

Introduction

Guillain-Barré syndrome (GBS) (65,119,148) is an acute polyneuropathy. It begins in a restricted area of the body, most often distally, and then spreads or ascends to involve many muscle groups. The rate and extent of progression vary widely. Many patients recover spontaneously without life-threatening progression. Some become severely paralyzed within a few days while in others the disease worsens slowly and insidiously over a period of several days or even weeks. The extent of paralysis varies widely. Sensory and autonomic nervous system involvement can also occur. In the most severely involved individuals, control of blood pressure and breathing maybe affected requiring a respirator and intensive care management. Progression of weakness usually ceases less than 4 weeks after onset. Spontaneous recovery usually begins within 2 to 4 weeks after progression stops. Recovery is usually gradual, but abrupt spontaneous recovery has been documented.

With current intensive care management under the most ideal conditions the mortality can be reduced to 5 percent or less. Prognosis for complete recovery is good, with about 85 percent of patients restored to normal function. The remaining usually have only mild residual deficits.

The etiology of GBS remains unknown. Cases have been associated with injection of foreign protein, cat scratches, dog bites, transfusions, and immunizations, including rabies vaccine and the widely publicized association with the 1976 influenza vaccine program.

Rumpl, et al. (119), have summarized the evidence as of 1981 for an immunologic mechanism as follows:

> Experimental allergic neuritis has shown striking similarity with the disease in humans. The immune pathogenesis of GBS was further supported by the finding of complement fixing antibodies, of precipitating antibodies against trypsinized white matter extracts and of myelinotoxin serum antibodies of the IgM class in patients with GBS. Cellular hypersensitization to peripheral nervous antigen presented by circulating immunoblasts and lymphocytes supported the role of cellular mechanisms in pathogenesis.

The rationale for the use of plasma exchange (PE) in GBS is based on the presence of serum antibodies which can be removed by PE.

Brettle, et al. (15), first reported the successful use of PE in acute GBS in 1978. An abrupt and dramatic improvement was seen in this case. This report was published shortly after Hughes, et al. (63), reported a poor response to steroids in a controlled clinical trial of acute GBS. With evidence against the use of steroids established in a controlled clinical trial and with evidence of a dramatic improvement with plasma exchange, many centers throughout the world began to experiment with and report their results of PE therapy.

The existing literature includes many case reports and small series of cases in which apheresis or more specifically PE was used in the treatment of acute GBS.

In reviewing this literature one must appreciate several factors repeatedly emphasized by the authors and critics.

1. As an experimental therapy initial use of the therapy was not standardized. The timing, quantity, duration, and type of PE varied considerably. In some patients the therapy was used concurrently with steroid treatment and in others after steroids had failed. Some patients were treated after extended respirator and intensive care therapy while others were treated in an effort to avoid the need for such care.
2. The measures of assessment of outcome also varied enormously. Some investigators reported obvious and at times dramatic clinical improvements while others reported changes in nerve conduction tests and immunological changes which preceeded or were unassociated with a clinical response.
3. The reported studies are all case reports without any concurrent control groups, blinding, randomization, or other techniques used in controlled clinical trials.
4. The documentation of adverse effects was not systematic and may have been biased by the tendency to report successful uses of a new therapy.
5. The natural history of acute GBS with its tendency for spontaneous and occasionally abrupt improvement makes the interpretation of therapy related results more difficult.

Despite these difficulties much has been learned from the initial studies and reports on the use of PE in GBS. The following section summarizes the reported evidence on efficacy.

Efficacy

The reported individual cases repeatedly refer to striking or dramatic change which occur within minutes to hours after plasma exchange.

One report (134) stated: "the improvement after the exchanges was so abrupt and striking that it induced us to believe that the plasma exchanges were essentially responsible for this development. Particularly in our case with ventilator insufficiency and bulbar palsy, which worsened day by day, the course of the disease seemed to have been reversed by plasma exchange inducing an immediate amelioration. The response was quicker in those nerves which had deteriorated the latest, which is in accordance with clinical experience in cases of spontaneous recovery."

Other cases of dramatic improvements after plasma exchange includes the following:

Littlewood and Bajada (77) report: "On day 8 of our patient's illness respiratory vital capacity fell to 1.41 and was accomplished by complete ophthalmoplegia and iridopligia. A dramatic improvement in vital capacity followed the first session and was subsequently maintained." Similarly, Corachan, et al. (27), report a case of: " . . . dramatic improvement after . . . (apheresis) . . . " Levy, et al. (76), report that "clinical improvement was dramatic" in a patient with chronic relapsing disease.

Not all investigators have reported success. Cook, et al. (26), reported a series of five patients only one of whom had a "significant clinical improvement. " Maisey and Olczak (78) reported two patients who failed to respond to PE. Gross, et al. (45), have argued that Maisey's use of 1.5 liters per day of plasma exchange was "small compared with those used by other operators for the same disease and in other disease processes." They further argue that one would not expect all cases to respond. They write: "Cases of inflammatory polyneuropathy probably constitute a heterogeneous group and it would be surprising if every patient proved to benefit from plasma exchange."

Several larger series have also been recently reported. Rumpl, et al. (119), reported eight cases of successful treatment with PE. They report: "Recovery was abrupt in all cases after the first PEs. Improvement was more marked, when . . . (apheresis) . . . was performed on three successive days with plasma exchanges of 2.0-3.01 each . . . . Recovery seemed to be delayed in cases when plasma exchanges were reduced to 0.5-1.51 each and were spread over several days or weeks, even when the number of plasma exchanges was increased."

Durward, et al. (33), reported their experience with six cases all of whom improved to some degree after PE. They conclude "Our experience to date (11 incidents in six patients) is of recovery beginning or accelerating immediately after plasma exchange . . . . We started exchanges fairly early-usually about one week after onset —and exchanged more than 10—1 on each occasion (except in case 3). "

Dau, et al. (31), report on 13 patients with acute GBS who underwent 2 to 3 weeks of PE with 4 or 5 exchanges of 4 liters. Seven patients, all of whom were still progressing or stable "stopped progressing on the day of the first . . . (apheresis) . . . and had discernible clinical improvement within 48 hours." Among the other patients two continued progressing, three were already slowly improving and apheresis "did not seem to accelerate recovery." In these patients apheresis was started "relatively late after disease onset ." In the last patient there was progressive deterioration. The report concluded that factors associated with a good outcome were:

1. Institution of apheresis early in the course of the illness.
2. Normal evoked muscle action potential.
3. Little electromyographic evidence of denervation.
4. Age less than 50 years.

Schooneman, et al.'s (123), series of 10 patients with acute GBS is the only reported series in which no patients received steroids and in which a control group was attempted. In addition, the authors performed extensive neurological testing before and after each exchange. Respiratory impairment was assessed by clinical examination and blood gas determinations.

In 9 of their 10 cases patients showed improvement within 24 hours after the first exchange. The authors believe that "the progressive phase of the disease was halted." They term their results "spectacular." In comparing their 10 patients to 258 historical control patients with GBS they conclude that apheresis appeared to shorten the duration of paralysis, reduce the need for tracheotomy, and shorten the hospital course. They did not demonstrate reduced mortality since one patient died in each group. They also did not demonstrate or claim that these patients represented comparable study and control groups.

Safety

Plasma exchange carries inherent risks in all patients. Samtleben, et al. (120), reporting on 100 consecutive PE procedures, observed allergic reactions to albumen in 10 percent, hypocalcemic symptoms in 6 percent, and vasovagal reactions in 5 percent. Other side effects have included massive extracorporeal blood clotting, hypercoagulation states with vascular thrombosis, hemorrhagic tendencies, changes in serum lipid

fractions, cardiac arrhythmias, and pulmonary emboli (93).

Rumpl, et al. (119), reported that in their experience with plasma exchange for GBS, cardiovascular problems, coagulation difficulties, and allergic reactions made it necessary to interrupt PE and influenced the amount of exchanged plasma.

Patients with severe GBS may have an unstable autonomic nervous system predisposing them to problems with blood pressure control and cardiac arrhythmias. The need to perform the procedure on respirator dependent patients may further complicate PE.

In light of these considerations Mayr, et al. (81), who have successfully used PEs in GBS, conclude: "The considerable risks and high technical requirements may limit this therapy to the severe course of Guillain-Barré syndrome."

Need for Controlled Clinical Trials

A controlled trial is not a trial of a treatment. It is a trial of a specific means of administering a therapy; thus it requires agreement on the timing, extent, and duration of therapy.

The performance of a controlled clinical trial should be preceded by enough research to establish an agreed upon method for administering the therapy. In addition, before going to the expense of a well-performed controlled clinical trial, it is important that preliminary evidence exists of the effectiveness and additional benefit of the treatment. These two prerequisites to a controlled clinical trial have been adequately fulfilled by the existing literature.

Despite the controversy in the reported literature over the efficacy and safety of PE in GBS, both the advocates and the skeptics appear to agree on the need for controlled clinical trials. A sampling of their comments should demonstrate this point.

Irvine and Tibbles (64) in their report of an apparently successful treatment with exchange transfusions conclude: "In the future it will be important to document failures as well as success to place this treatment in its proper perspective. It is likely that the organization of a prospective controlled trial of this costly form of management will be necessary."

During 1981 a series of letters appeared in the *British Medical Journal* reporting dramatic improvement, evidence of subtle response, and cases without measurable improvement. All three reports agreed on the need for a controlled trial. The group (78) reporting no response wrote: "If anecdotal reports are relied on, publication bias ensures that apparently successful results dominate the literature." The group (62) reporting success wrote: " . . . a controlled trial of plasma exchange is necessary in acute inflammatory polyradiculoneuropathy before its value can be assessed. Since patients with this condition begin to improve after a variable time after the onset of symptoms and usually recover completely, it is not surprising that each new treatment has been hailed with enthusiasm on the basis of anecdotal reports." The group (33) reporting subtle responses concurred, stating: 'These data only reemphasize the need for a controlled clinical trial, especially in the early phase, in order to delineate the role of plasma exchange in acute Guillain-Barré syndrome."

In their advocacy of their forthcoming controlled clinical trial Asbury, et al. (10), wrote in the October 1980 issue of *Neurology* that apheresis of "an acutely ill patient with respiratory depression and autonomic instability is not a benign procedure. Until this study is completed anecdotal reports of the efficacy of . . . (apheresis) . . . in the Guillain-Barre syndrome should be interpreted with caution. At present, it is not possible to state the therapeutic role that . . . (apheresis) . . . plays for this disease,"

Controlled Clinical Trials in Progress

In December 1980, the National Institute of Neurological and Communicative Disorders and Stroke funded a 3-year multiple site cooperative study of apheresis treatment of acute GBS (87).

The primary study question is: Does apheresis effect a significant beneficial change in the early course of severely ill patients with GBS? Secondary study questions include the following:

1. Are there clinical, epidemiologic, laboratory, or electrodiagnostic factors associated with a good outcome of GBS? If so, how does apheresis interact with these factors?
2. Is there a subgroup of patients with GBS for whom apheresis can be expected to be of value and a subgroup for whom it cannot?
3. Can apheresis reduce the incidence of long-term complications (assessed at 6 months) in the 15 to 20 percent of GBS patients destined to have some lasting deficits?

The study uses generally accepted criteria for the diagnosis of GBS. Patients must be within 30 days of onset of definitive neuropathic symptoms. They must require a walker or support to walk 5 meters or be more severely affected. Steroid treatment is not given to study patients. The quantity and timing of the PE are consistent with that reported for successful uses of PE in GBS.

The study protocol provides standard methods for assuring randomization, informed consent, termination, monitoring of followup, and statistical analysis.

The study is designed to include about 240 patients. This number is adequate to provide an 80-percent chance of demonstrating a statistically significant improvement if apheresis actually provides a 50-percent improvement over conventional therapy. As of July 1, 1982, 102 patients had been enrolled in the study.

An interim analysis of the data is planned when approximately 120 patients have been entered into the study. The interim analysis is designed to determine whether the study should continue. This analysis will consider the following three possibilities:

1. The evidence is overwhelming that the apheresis patients are doing better, and if the study were to continue with little or no advantage to the exchange protocol over the second half of the study, a statistically significant difference would still exist.
2. the exchange protocol patients are doing worse or no better than the other patients and continuation of the study could not, even with an extreme reverse of results in the second half, demonstrate a beneficial effect of apheresis.
3. Neither extreme exists.

The endpoints considered in this analysis will be measures of clinical improvement 4 weeks after entry into the study as well as time spent on a respirator. If the interim report reaches conclusion 1 or 2, the study will be stopped and presumably the results released and reported. Otherwise the study will continue and the results presumably will not be released by the National Institutes of Health (NIH).

The NIH study appears to be adequately designed to answer the basic questions regarding efficacy of apheresis. The results should largely determine whether evidence exists for moving PE from an experimental status to that of a conventional therapy for acute GBS.

A second randomized controlled clinical trial is currently underway in Great Britain (87). This study also includes patients who require support to walk 5 meters or who are more severely affected. The findings on the first 19 randomized patients were reported in May 1982. A "decided trend in favor of plasma exchange was noted at 4 weeks after randomization which did not reach statistical significance."

NIH will not currently release preliminary results of the American study. The interim analysis should be completed by early 1983, but unless the results of the interim analysis clearly answer the efficacy question, a full report may not be available until 1984.

Conclusions

1. Case reports and small-scale, mostly uncontrolled trials provided suggestive evidence that plasma exchange may be efficacious for some patients with acute GBS.
2. Because of the low mortality and good prognosis for most patients with Guillain-Barré syndrome, the safety of the procedure and indications for its use should be delineated prior to nonexperimental use of plasma exchange in GBS.
3. The conditions for use of plasma exchange in acute Guillain-Barré syndrome have been sufficiently standardized to enable a controlled clinical trial of the procedure.
4. The potential cost saving and potential for shortened disability make well-designed controlled studies of this therapy important.
5. Controlled studies of the efficacy, safety, and indications for plasma exchange in acute GBS are currently in progress. These studies should be adequate to provide data which address the essential clinical questions. Until the results of these studies are available, the use of plasma exchange in GBS should be considered an experimental procedure.

Appendix E.—The Cause and Pathological Development of Autoimmune Diseases*

The cause and pathological development of autoimmune diseases are thought to be due to several mechanisms, each having varying importance in different diseases. These mechanisms are: inactivation reactions, cytotoxic reactions, immune complex deposition, anaphylaxis, and delayed hypersensitivity.

With inactivation reactions, autoimmune antibodies are directed against molecules that are receptors or mediators for important physiological functions. For example, people with myasthenia gravis have antibodies directed against neurotransmitter receptors on muscle membranes, and thus the conduction of electrical impulses between nerve and muscle is disturbed.

In diseases in which cytotoxic antibodies are thought to play a role, antibodies are directed against molecules on the surface of cells, and reactions between the antibodies and antigens result in the killing of the cells through complement mechanisms or clearance by lymphoid tissues. This can lead to depletion of sets of cells required for vital functions, such as platelet loss in idiopathic thrombocytopenic purpura.

In many diseases, deposition of immune complexes in tissues is thought to be the mechanism for the destructive lesions observed. These immune complexes may consist of antibodies and viral antigens, cancer antigens or other antigens. In these diseases, the complexes are of such a nature or in such great amounts that they saturate the normal clearing system in lymphoid tissues (or these clearing systems are deficient secondary to the underlying disease). Deposition of the complexes in vessel walls, in structures of the kidney, and joint spaces leads to inflammation due to the activation of complement or cellular immune responses. Vasculitis, glomerulonephritis and arthritis, for example, can be the result.

Anaphylaxis refers to the release by antigen stimulation of immediately reacting inflammatory agents by tissue cells which have antibodies directly on their surfaces. Severe anaphylactic reactions are life threatening. Diseases that are manifested by anaphylactic reactions include food allergies, insect allergies, and asthma.

Finally, there are diseases transmitted by cellular immune mechanisms, referred to as delayed hypersensitivity reactions. In this case, specifically, sensitized lymphocytes infiltrate tissues and cause destruction. Often circulatory antibodies participate in the process as well. Examples of this disorder include viral hepatitis and graft rejection.

● This appendix is condensed from Frost & Sullivan, Inc., ***in-Vivo Hemodetoxification and Hemoprocessing Markets in U. S., New*** York, June 1981.

Appendix F.—American Red Cross Bibliography

This appendix contains a Therapeutic Apheresis Bibliography that was compiled by the American Red Cross and is distributed to American Red Cross regional blood services to facilitate access to current information on therapeutic apheresis by specific disease categories.

The bibliography is divided into two sections. The first section contains 1,241 citations that comprised the apheresis literature as of May 1982. The second section is a supplement that adds 778 references through January 1983 to the original list.

References in both sections are listed by reverse chronological order and grouped by specific disease categories. Some articles may be cited in more than one category if their content warrants multiple listings. Texts, symposia, and review articles (sec. XVII) may also contain information pertinent to specific diseases, but some of these summary publications may not be listed by disease category.

AMERICAN RED CROSS BLOOD SERVICES

BIBLIOGRAPHY OF THERAPEUTIC PHERESIS* BY DISEASE CATEGORIES

No. 1: Neurological Disorders

- A. Myasthenia Gravis
- Multiple Sclerosis
- : : Refsum's Disease
- D. Guillain-Barre Syndrome
- E. Miscellaneous: Polyneuropathy, Motor Neuron Disease, Amyotrophic Lateral Sclerosis

No. II: Blood Diseases

- A. Hemophilia
- B. Autoimmune Hemolytic Anemia
- C. Aplastic Anemia
- D. Immune Thrombocytopenic Purpura
- E. Thrombotic Thrombocytopenic Purpura, Hemolytic Uremic Syndrome
- F. Sickle Cell Disease
- G. Leukemia, Myeloproliferative Syndrome, Sezary Syndrome
- H. Thrombocytosis
- L Miscellaneous

No. Ill: Malignant Paraproteinemias

- A. Hyperviscosity Syndrome "
- B. Macroglobulinemia
- C. Multiple Myeloma
- D. Cryoglobulinemia
- E. Miscellaneous

No. IV: Renal Diseases

- A. GoodPasture's Syndrome
- B. Glomerulonephritis
- C. Miscellaneous

No. V: Connective Tissue Disorders

- A. Systemic Lupus Erythematosus
- Polyarteritis Nodosa - Wegener's Granuloma
- : : Rheumatoid Arthritis
- D. Raynaud's Syndrome
- E. Miscellaneous

No. W: Transplantation

- A. Renal
- B. Bone Marrow

No. VU: Liver Disease

- A. Hepatitis, Hepatic Coma
- B. Miscellaneous

No. VIII: Hemolytic Disease of the Newborn

No. Ix: Cancer

No. X: Skin Diseases

- A. Pemphigus Vulgaris
- B. Erythrocyte Autosensitization
- C. Miscellaneous

No. X1: Lipid Disorders (Hyperlipidemia)

No. XII: Immunological Disorders

- A. Immunodeficiency
- B. Immune Complex Disease

No. XIII: "Miscellaneous Diseases

- A. Thyroid Storm
- B. Pulmonary Edema, Adult Respiratory Distress Syndrome
- C. Hypertension
- D. Poisoning
- E. Asthma
- F. Crohn's Disease
- G. Miscellaneous

No. XIV: Clinical Reactions, Complications

No. XV: Technical Aspects

No. XVI: Alternative Methodologies

No. XVII: Texts, Symposia

*l'his Case Study has used the term "apheresis" throughout its contents for the purpose of consistency. However, the term "pheresis" is used by the American Red Cross with the same meaning.

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Supplement 2

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Supplement 2

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Supplement 2

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Supplement 2

Therapeutic Pheresis Bibliography No. X: Skin Diseases

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