

# **Introduction and Summary**

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## 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 Laborato-

ries, 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.

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 (Waldenström’s) and hyperglobulinemias, including multiple myeloma. There is certainly suggestive evidence, too, that therapeutic apheresis is successful in arresting the disease process for some patients 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 monoclonal 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 be an 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 form a 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. )