Evaluation of the Utilization of Human Blood Resources in the United States (1970)

Pages
60

Size
5 x 9

ISBN
030936079X

Ad Hoc Committee on Component Therapy; Committee on Plasma and Plasma Substitutes; Division of Medical Sciences; National Research Council

In 1967, a group of business and professional people joined in an effort to accelerate the diffusion of knowledge and techniques in the field of blood-component therapy. Convinced that the more widespread use of blood components would help to provide better therapy, make better use of the national blood supply, and lower medical costs, they began searching for ways to bring about the wider application of principles and technology that have been known to and accepted by the scientific world but have been applied only in isolated areas.

These people organized the Component Therapy Institute. The Institute is a non-profit corporation whose objective is to "promote the utilization of scientific and technological advances in the collection, preservation, treatment, dissemination and distribution of blood and its component parts to patients, hospitals, doctors, and others engaged in the collection, preservation, treatment, dissemination and distribution of blood and its component parts." The Institute neither overlaps nor duplicates any known organization; and it seeks no funds from the general public.

After making an extensive investigation of current activities in the field of blood banking and utilization, the Institute concluded that an impartial and objective study would be necessary. Through such a study, an attempt would be made to define problems and provide direction for the future efforts of the Institute and perhaps for other groups with specific interests in the overall blood-resources structure.

In September 1969, the Institute asked the National Academy of Sciences–National Research Council to undertake this study. Members of the Board of Directors of the Component Therapy Institute are:

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An Evaluation of the Utilization of Human Blood Resources in the United States

Prepared by

ad hoc Committee on Component Therapy
Committee on Plasma and Plasma Substitutes

Division of Medical Sciences

National Academy of Sciences–National Research Council

Supported by

Component Therapy Institute

October 1970

copies of the report are available from

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Preface

In September 1969, the Component Therapy Institute, organized "to promote the utilization of scientific and technological advances in the collection, preservation, treatment, dissemination and distribution of blood and its component parts to patients, hospitals, doctors, organizations, or others engaged in the collection, preservation, treatment, dissemination and distribution of blood or its component parts," asked the National Academy of Sciences–National Research Council to recommend ways in which the above goals could be reached and to determine the Institute's appropriate role in reaching them. For that purpose, the Division of Medical Sciences established an *ad hoc* Committee on Component Therapy, whose membership reflected a variety of experience and viewpoints with respect to the collection and use of blood.

At an early meeting of the nucleus of the Committee, it was determined that the interests of the Institute—and the public—would be served best by a broad assessment of the manner in which the nation's blood resources are utilized. This assessment was intended primarily to identify areas in which the application of modern scientific, technologic, and operational advances would permit more efficient utilization of blood and provide greater benefit to the patient population. In the course of this assessment, the Committee drew upon the resources of its members, reviewed published and unpublished data, and held informal consultations with knowledgeable persons in specific fields. It soon became apparent that reliable, comprehensive data were largely lacking in all areas of activity of the blood-service complex. The Committee therefore chose to draw broad conclusions, on the basis of the evidence that was available, with respect to potential areas of improvement and to make recommendations that it is hoped will lead to the rational and orderly improvement in the areas identified.

This report is intended to be chiefly a basic document to inform the Component Therapy Institute and other concerned members of the community of the nature of the blood-service complex in the United States and to suggest areas in which lay leadership and support can best contribute to the enhancement of this resource.

Summary

THE PROBLEM

Blood is a unique human resource to which dollar values cannot realistically be ascribed. The therapeutic benefits derived from the human blood collected in the United States fall far short of its potential value to the patient population. The reasons for the gap are diverse and originate in all phases of the blood-service complex—procurement, processing, distribution, and utilization of blood and blood products. The discrepancy is due in part to the failure of a substantial portion of the medical profession to adopt proven concepts of component therapy and in part to a lack of integration among the private and governmental agencies involved in the provision of blood services.

SOLUTION OF THE PROBLEM

By the application of available knowledge, the effectiveness of this limited national resource can be markedly amplified through its division into multiple components having specific therapeutic effects, and through better patterns of distribution and utilization. The problem is soluble. In the national interest, it must be attacked. In the opinion of the Committee, it can be dealt with most effectively at a national level through an undertaking of comprehensive scope. The ultimate creation of a body that could bridge the gap between the private and governmental sectors should be considered. Such a body should ensure (1) an orderly integration of the services performed by diverse operating agencies, (2) the stimulation of technical and scientific advances, and (3) the early application of new knowledge in the field.

ANTICIPATED REACTIONS TO PROPOSALS FOR CHANGE

In the absence of a national structure within which to work, diverse agencies have attempted to meet immediate and sometimes parochial needs, occasionally with inadequate concern for the broader national need. These agencies have, understandably, developed vested positions, which must be taken into

consideration when the establishment of a new body to develop an integrated national blood program is contemplated. Although some resistance might be expected, it is anticipated that the separate agencies will recognize that the potential benefits of the new structure outweigh the possible disadvantages of their participation in it.

FUTURE POTENTIAL

After 30 years of growth, the science and practice of blood transfusion are still in a relatively early stage of development. The value of many components of human blood remains inadequately explored and largely unexploited. They hold promise of opening new directions in the clinical management of a wide variety of disease states. A truly national blood program could remove many of the restraints that now impede the realization of this potential.

Contents

Therapeutic Aspects of Blood

GENERAL THERAPEUTIC USES OF BLOOD

Blood consists of formed elements (red cells, white cells, and platelets) and plasma, the fluid that remains after removal of the formed elements and contains a number of noncellular elements.

From the physiologic standpoint, one can ascribe three broad roles to blood:

(1) Functions that are unique to its components and exercised for the most part within the circulatory system, such as the transport of oxygen and carbon dioxide, the ingestion and destruction of infectious organisms, and coagulation.

(2) The transport of nutritional materials and metabolic products between appropriate cells and tissues, such as the distribution of proteins and hormones and the delivery of waste products to the kidney.

(3) The self-serving activity of promoting the hydrodynamic efficiency of the circulatory system by maintaining appropriate volumetric and rheologic properties.

Human blood itself is a life-saving therapeutic agent in some circumstances, but it is also the only available raw material for a number of preparations in great demand for the preservation of life for a few and the preservation of health for many. The most critical aspect of the supply of blood is that it can be obtained only from human donors. As the therapeutic applications of blood and its derivatives have expanded, the medical community has taken steps to meet the growing demand. Blood is being prescribed in a more rational manner; for example, fewer single-unit transfusions (which are rarely justifiable) are being administered. There is widespread use of volume-expanding fluids other than whole blood in the treatment of shock. The technique of plasmapheresis, which permits a donor to contribute large amounts of plasma without being deprived of his red cells, has been widely adopted as a source of plasma, from which a number of important products may be prepared. Nevertheless, supply and demand remain in critical balance.

Whole blood has been used with great effect for many years. The use of fresh blood can offer all the benefits listed below. In many cases, however,

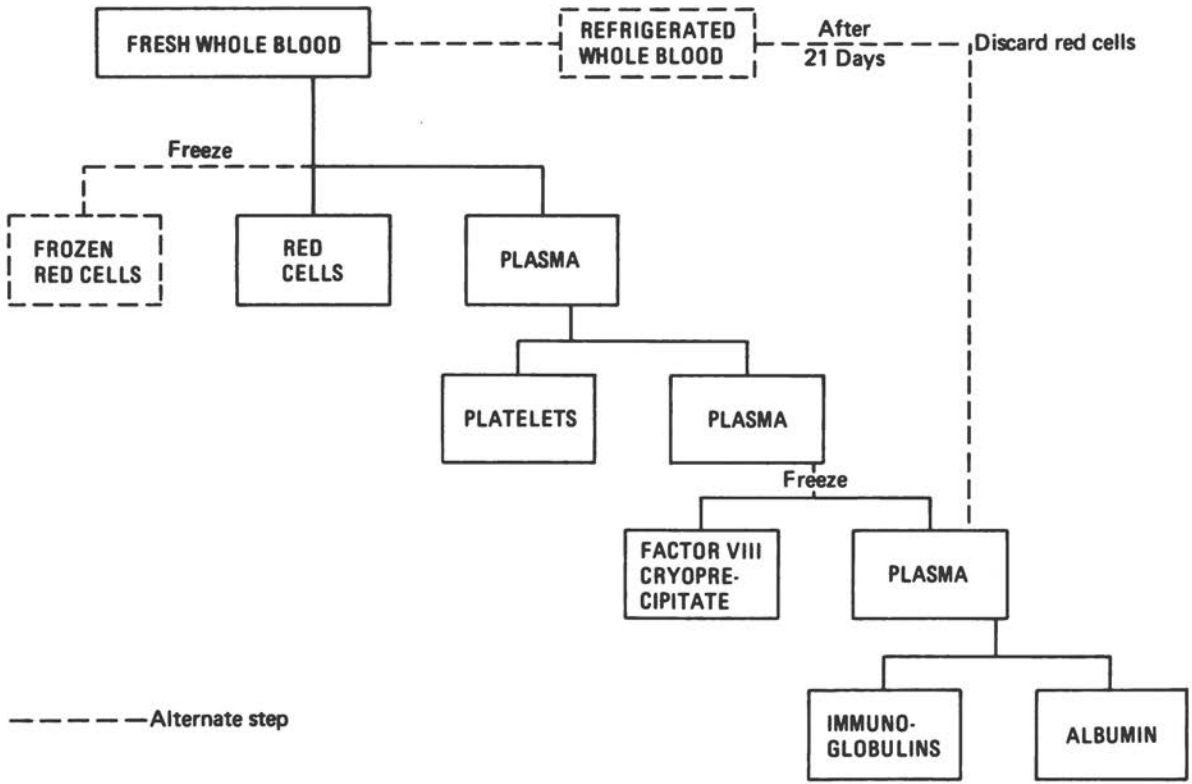

FIGURE 1. Common scheme of blood processing.

the volume of whole blood required to provide an effective dose of a specific component is physiologically prohibitive. The administration of whole blood for the effect of but one of its components frequently subjects a recipient unnecessarily to the risk of complications arising from other components or agents included therein. The major therapeutic applications of blood are as follows:

(1) *Oxygen transport.* The transport of oxygen is basically a function of the red blood cells. They are effective for this purpose when administered in any of a number of isotonic electrolyte or oncotic solutions.

(2) *Coagulation.* Blood contains platelets and approximately 12 different coagulation factors, which are useful in treating coagulation disorders. Normal blood clotting requires the interaction of the platelets and more than a dozen protein or other chemical constituents of the plasma. Of the protein constituents, factor I (fibrinogen) and factor VIII (antihemophilic factor, or AHF) are most frequently used.

(3) *Defense against infection.*

(a) *Immunoglobulins.* The specific antibodies which develop as a result of invasion by pathogenic organisms or introduction of foreign material (for example, Rh-positive red cells into an Rh-negative person) are contained in the immunoglobulin fraction of plasma. Gamma globulin prepared from the blood of normal donors is capable of protecting patients with the most common type of immunoglobulin deficiency from severe bacterial infections. In some circircumstances, gamma globulin with a very high content of antibody to a specific agent can be identified or produced.

(b) *White blood cells.* Of the white blood cells, the granulocytes appear to have beneficial effects when administered to patients suffering from disease processes that have effectively eliminated their own white cells.

(4) *Maintenance of blood volume.* The dynamic efficiency of the circulatory system depends on the resistance or tone of the vascular bed (including the propulsive force of the heart) and the circulating fluid volume. Blood, by volume, is roughly half plasma and half red cells. Insofar as volume replacement alone is concerned, liquid plasma, plasma albumin, and some colloidal and electrolyte solutions are at least as effective as the red cells.

SPECIFIC AVAILABLE THERAPEUTIC BLOOD PRODUCTS (Fig. 1)

Whole Blood

Whole blood is generally packaged as units of approximately 500 ml in disposable plastic or glass containers. Each package contains a solution that prevents coagulation and minimizes deterioration of the red cells. The most

widely used anticoagulant-preservative is an acid-citrate-dextrose (ACD) mixture first introduced in 1943. Blood containing ACD and stored at 1–4°C may be used for up to 21 days. The proponents of a citrate-phosphate-dextrose (CPD) formula developed in 1961 claim that it extends the effective shelf-life of the red cells to 28 days, lessens the acid load on the recipient, and improves oxygen release. The widespread adoption of CPD has been delayed because clinical investigations have not been sufficient to convince the responsible federal regulatory agency that it should license CPD blood for more than 21 days. Nor is that agency ready to license immunoglobulins prepared from blood collected in CPD, despite their clinical use by more than one state health agency. The addition of adenine to ACD and CPD has produced two experimental solutions that maintain the useful function of red cells for 34–42 days. The further addition of the nucleotide inosine to these solutions after 18–20 days of refrigerated storage restores the metabolic state of the red cells to that of cells stored for only 5 days.

The glycolytic intermediate compound 2,3-diphosphoglycerate (2,3-DPG) in red cells is important in the metabolic systems that maintain cellular integrity and allow hemoglobin to release oxygen to tissue at physiologic levels of partial oxygen pressure. Recent studies indicate that the level of 2,3-DPG in ACD blood stored at 2–4°C falls to low levels by the fifth day of storage. However, because the 2,3-DPG content and the oxygen dissociation curve recover within 12 hr of infusion, the defect appears to be important only in acutely hypoxic patients who require large amounts of blood. Blood preserved in CPD maintains adequate 2,3-DPG levels for as long as 10 days.

Red-Cell Preparations

When blood is drawn into multiple plastic packs, the red cells can be aseptically separated from the plasma, platelets, and white cells. Of such preparations, the Committee on Transfusion and Transplantation of the American Medical Association has said:[4]

> Transfusion of red blood cells (also referred to as concentrated, packed, or enriched red blood cells) rather than whole blood, is generally the best and safest method of fulfilling a patient's need for increased oxygen-carrying capacity, whether that need results from chronic anemia or acute blood loss. A routine request for 'blood' might well imply red blood cells rather than whole blood. The routine use of whole blood can no longer be justified.
>
> Red blood cells are ordinarily prepared from the whole blood simply by removal of most of the donor plasma (which can then be used in the preparation of other components), leaving the red blood cells suspended in a smaller volume of plasma and resulting in hematocrit values of from 60% to 80%. Red blood cells properly prepared in this way have the same shelf-life as does whole blood.
>
> The advantages of red blood cell transfusions are:
>
> 1. The risk of circulatory overload is reduced. Circulatory overload is a major problem, particularly in elderly patients and those with severe chronic anemia.

2. The risk from metabolic by-products which accumulate in plasma during storage of whole blood (such as lactic acid, potassium, inorganic phosphate, and ammonia) is reduced.
3. The risk of reactions to allergens and antibodies in plasma is reduced.
4. The risk of reactions to plasma protein antigens is reduced in multitransfused recipients.

Red blood cells may be supplemented by balanced salt solutions or plasma expanders in the treatment of hemorrhagic shock.

Specific bleeding defects are best corrected by the administration of the appropriate blood component concentrated, e.g., platelets, antihemophilic factor (Factor VIII).

Red blood cells, rather than whole blood, are preferred for priming renal dialysis units and for partial or complete priming of extracorporeal heart-lung circuits.

It is likely that from 60% to 80% of blood transfusion needs can and should be met by use of red blood cells (rather than whole blood).

The basic purpose of separating red cells is to recover the maximal percentage of red cells with minimal amounts of other cells and plasma. Simple sedimentation is the least efficient method of achieving this purpose. Depending on the degree of "purity" required, more complex techniques, including washing the cells may be used. Red cells prepared in a closed system with at least 20% of the original plasma can be stored for 21 days at 4°C. If the separation techniques raise the possibility of introducing bacterial contaminants, the red cells are infused within 24 hr. If the technique removes more than 80% of the plasma, and thus threatens the nutrition of the cells, the preparation is administered within 3 hr.

Red cells may be preserved for long periods by a number of freezing techniques. For example, red cells frozen at −85°C with a protective additive, such as glycerol, have been shown to be viable on thawing after a storage period of 10 years. Thawed and washed red cells are accompanied by minimal numbers of leukocytes and platelets and essentially no residual donor plasma. Cells stored at −85°C do not undergo 2,3-DPG depletion. The expense of this technique and the time consumed in removing the additive before infusion have delayed its adoption on a wider scale. Its prospect as a means of overcoming red-cell waste due to outdating and eliminating dependence on day-to-day blood collection is attractive. The freezing process is now used for the maintenance of a supply of red cells suitable for administration to patients who have rare or complex blood-group patterns, the storage of a patient's own red cells in anticipation of elective surgery, the maintenance of a backup supply of cells for use when normal supplies are inadequate, and the administration of red cells without plasma proteins or leukocytes. The removal of leukocytes from blood to be given to transplant recipients lessens posttransplant rejection phenomena.

Concentrated Leukocytes

Depletion of functional leukocytes in patients with leukemia or other leukopenic states leads to overwhelming infection. An adequate replacement of these

short-lived cells would generally require the frequent administration of the leukocytes from 30-40 units of normal blood. In the present circumstances, that is not feasible. However, the great excess of white cells in the blood of patients in some stages of chronic myelocytic leukemia makes them a possible source. Because the infusion of leukemic cells is not without possible hazard, techniques for the collection of large volumes of normal leukocytes are being developed for use in cases of reversible bone marrow failure.

Platelets

Platelets are used to overcome such quantitative deficiencies as may be found in secondary thrombocytopenia. Therapeutically effective numbers of platelets cannot be administered in whole blood. But platelet-rich plasma, which contains 90% of the platelets and only half the volume of the original unit, and platelet concentrates, which contain 70%–80% of the platelets in 5% of the volume, are useful products.

Plasma

Plasma may be obtained from a unit of whole blood or by plasmapheresis. The latter procedure, because it involves the separation and return to the donor of his red cells, permits the collection of 500–1000 ml of plasma each week from one donor. For the full potential of plasma from a unit of whole blood to be realized, it must be separated from the cells on the day of collection. If it is separated later, it is in general suitable only for the preparation of albumin and globulin.

The basic process now licensed by the federal government for the fractionation of plasma was introduced 30 years ago. Newer fractionation processes have led to sharper separation of components, and thus increased yields, but they have not yet been adapted to use on an industrial scale. There is a need to reduce the loss of various components that results simply from the mechanics of handling the plasma. Only 55%–60% of the original gamma globulin and 40%–50% of the albumin are actually retrieved. Loss of perhaps 10% of the original material must be considered unavoidable—small portions that remain in tanks and centrifuges, that which remains in sterilizing filters at the end of the filtration process, and the overfill which must be added to bottles in order that the labeled quantity may be withdrawn. Moreover, in the current process, the fractions are not separated sharply. The main component of a given fraction is generally accompanied by other components that must be removed and discarded in the process of purification. The exercise of very careful control at each step of fractionation will result in slightly increased yields, but this potential is limited in the current process.

Single-donor plasma consists of approximately 220 ml of plasma obtained from a single unit of blood and stored in the liquid state at room temperature, frozen, or freeze-dried. It is generally prepared from blood that has been stored for some time. Therefore, because some of its components have deteriorated, it is recommended chiefly for the expansion of plasma volume, as in burns and the emergency treatment of shock due to hemorrhage.The use of the term "single donor" implies that the product carries the risk of infection only of a single unit of blood, rather than the risk associated with the pooling of blood from many donors. Single-donor fresh-frozen plasma, placed in a $-30^{\circ}C$ freezer within 4 hr of collection, has the therapeutic properties of fresh plasma, with the advantage that its components retain their effectiveness for at least a year in storage.

Plasma Fractions

Single-Donor Factor VIII-Rich Cryoprecipitate When fresh-frozen plasma is thawed at $4^{\circ}C$ and subjected to centrifugation, a cold-insoluble fraction that contains about 50% of the original factor VIII (about 130 AHF units) in less than 3% of the plasma protein may be recovered. This product is of prime importance in cases of classical hemophilia; the relatively low volume per unit dose permits intensive treatment without danger of overloading the patient's circulatory system. The AHF content, which is not indicated on the package, may range from 70 to 180 units.

Lyophilized Superconcentrate of Factor VIII Freeze-dried commercial preparations of factor VIII may contain from 125 to 1000 units of AHF. They have been assayed, and each vial is labeled with its AHF content. Some of these products may be kept at room temperature for long periods. Because the concentrates are prepared from large pools of fresh plasma, they are associated with a higher risk of hepatitis than single-donor plasma or cryoprecipitate. The manufacturer is able to recover less than 50% of the theoretical yield. The largest single loss occurs between the collection of plasma from the donor and the pouring of plasma into tanks for fractionation. A great contribution to solving this problem would be the discovery of an AHF-stabilizing agent that would have no deleterious effect on other plasma components and that in trace amounts would not be harmful to patients.

Factor IX Complex Factor IX complex is a fraction of plasma containing coagulation factors II, VII, IX, and X. It is of special benefit to patients with hemophilia B (Christmas disease) and those with liver disease, in whom deficiency of multiple coagulation proteins not infrequently causes hemorrhagic

complications. Like the factor VIII concentrate, factor IX complex is prepared from pooled plasma and poses a high risk of hepatitis.

Fibrinogen (Factor I) Fibrinogen is used when bleeding is due to lack of fibrinogen. It is stable only in fresh whole blood or fresh-frozen plasma. It can be concentrated and stored in the liquid state, but it is subject to precipitation. Stable dried concentrates have been prepared commercially. Of the blood products, fibrinogen prepared from pooled plasma carries the greatest risk of viral hepatitis, despite the application of partial sterilization techniques.

Immune Serum Globulin Immune serum globulin is a solution of the gamma globulin fraction of pooled plasma. It contains antibodies to many of the infectious agents to which the donor population has been exposed. It is effective in cases of congenital gamma globulin deficiency and in the prevention or attenuation of measles, poliomyelitis, and infectious hepatitis. Although it is prepared from pooled plasma, immune serum globulin appears to be free of the risk of transmitting serum hepatitis.

Specific Immunoglobulins It is possible, by selecting donors in a postinfection state or by subjecting selected persons to hyperimmunization, to produce a gamma globulin fraction with such a high titer of antibody to a single disease that it may be called "specific." These forms of immunoglobulins are of value in passive immunization against, and sometimes in the therapy of, tetanus, whooping cough, mumps, chickenpox, herpes zoster, rabies, and the complications of smallpox vaccination. Although there is little demand in this country today for the gamma globulin derived from normal plasma, there is growing interest in the specific immunoglobulins. Most manufacturers working in the field are pursuing several paths of research in the hope of substantially increasing the supply of these plasma components and the number of infectious agents subject to control by them. Of particular interest is the finding that the administration of an anti-Rh factor antibody to an Rh-negative woman within 72 hr after delivery of an Rh-positive baby prevents her from forming her own anti-Rh antibodies. This discovery should permit a marked reduction of the serious forms of the "Rh disease," erythroblastosis fetalis.

Improved methods of immunoglobulin separation suggest that concentrates of immunoglobulin A could be made available for the specific therapy of infectious problems of the gastrointestinal tract and mucous membrane surfaces. Concentrates of immunoglobulin M could also be made available for the therapy of Pseudomonas infections, whose incidence has increased sharply with the increasing use of chemotherapy in the management of acute leukemia.

Albumin Plasma albumin is available as a 5% buffered saline solution or a 25% "salt-poor" form. These products have been heat-treated to inactivate the hepatitis agent(s). They may be used in the treatment of shock due to hemorrhage, trauma, or infection and for the replacement of protein in burns or other protein-deficiency states. Albumin may be administered in conjunction with red-cell preparations for the treatment of hemorrhagic shock.

Plasma-Protein Fraction Plasma-protein fraction is a commercial preparation of plasma from which the gamma globulin and fibrinogen have been removed. It is used for the same purposes as the 5% albumin preparation.

It is important to note that, if one is to take full advantage of the potential of a unit of whole blood, the decision to separate the red cells from the plasma must be made shortly after collection. Whole blood drawn from a donor may be administered as such at any time within a specific dating period. For the anticoagulant-preservative currently in general use, that period is 21 days. However, to be used most efficiently, the blood should be separated, within 4 hr of collection, into packed red cells (which can be used within the 21-day period or frozen for indefinite storage) and platelet-rich plasma. The platelets (which must be used within 72 hr) and the leukocytes (which must be used within 24 hr) can then be separated from the plasma. The residuum may be stored as fresh-frozen plasma or used as a source of cryoprecipitate. If cryoprecipitate is removed, the residual plasma may be pooled for eventual fractionation into albumin, gamma globulin, and fibrinogen. Depending on the requirements of the specific system used, any of several fractions can be obtained, but no one anticoagulant-preservative is optimal for all products. It is unfortunate that the large volume of blood collected by mobile units, the majority of which are not yet equipped to separate and freeze the plasma, cannot be fractionated in this way.

Hazards of Transfusion of Whole Blood

Blood is potentially hazardous when infused, because of its antigenic properties, the possibility that it may harbor infectious agents of donor origin or introduced during processing, and the fact that, being readily subject to deterioration, it may contain harmful products of that deterioration. In some clinical circumstances, the volume alone can be deleterious to the patient.

INFECTION

Of the infections that may be transmitted by transfusion, hepatitis is the most important. The incidence of transfusion-associated (serum) hepatitis varies widely, depending particularly on the care with which donor screening is carried out and the region of the country or the community in which the transfused blood was collected. Two recent developments show promise of reducing the hepatitis risk associated with transfusion: the development of increasingly sensitive methods for detecting the Australia (hepatitis-associated) antigen suggests that hepatitis carriers in the donor pool may be recognizable in time to eliminate their blood from therapeutic use, and a recent study of the effectiveness of "transmembrane" red-cell washing suggests that frozen red cells resuspended in electrolyte solution or in sterilized oncotic solution (albumin) are essentially free of contaminating viruses.

Among other infections related to *fresh* whole-blood transfusion are those attributed to the cytomegalovirus and the Ebstein-Barr virus. Like the virus(es) of hepatitis, these agents may be present in the blood of donors who have no clinical signs of illness.

Of the nonviral diseases that are now occasionally transmitted by transfusion, malaria and syphilis are the most important.

ANTIGEN-ANTIBODY REACTION

In 55% of persons of European origin, the red cells contain one or both of two specific antigens, termed A and B. The plasma of the 97% of such persons who have but a single antigen contains antibodies to the other antigen. The

major antibodies are termed anti-A and anti-B. Thus, group A blood possesses the cellular antigen A and the plasma antibody anti-B. If group A blood is given to a group B patient, the antigen-antibody reaction destroys the donor red cells and may be fatal. Although careful testing of donor and recipient blood can eliminate that hazard, the existence of many other specific, but less antigenic, blood-group substances, including those of the important Rh system, makes it almost impossible to eliminate all immunologic reactions in patients who receive multiple transfusions of whole blood or red cells. In addition to the antigenic properties of the red cells, immunologic transfusion reactions have been attributed to donor white blood cells, platelets, and a number of plasma proteins.

FOREIGN CHEMICALS

The anticoagulant-preservative commonly added to donor blood has a tendency to increase the acidity of the blood of the recipient and to bind calcium that is needed for cellular-membrane function. Those effects are important only when large volumes of donor blood are administered rapidly, as in the treatment of a massive hemorrhage or in "exchange" transfusions. In such circumstances, a state similar to diabetic acidosis and calcium deficiency may occur and require treatment. Also, there may well be chemical substances in the blood of the donor, such as hormones and split plasma-protein fractions, that could affect the patient.

EFFECTS OF CELLULAR METABOLISM AND PROTEIN DENATURATION

When whole blood is stored under refrigeration, metabolic by-products accumulate in the plasma. These products—such as lactic acid, potassium, inorganic phosphate, and ammonia—may have a harmful effect on the condition of a patient whose electrolyte balance is already tenuous.

EXCESS VOLUME

The oxygen-carrying capacity of donor red cells may be required, for example, in a patient with chronic anemia whose heart is failing. If these red cells are administered in whole blood, the relatively prolonged increase in blood volume contributed by the unneeded plasma may cause further decompensation of the heart. Although there is some evidence that this effect may be due to

pressor substances in the plasma, and not entirely to volume itself, the fact remains that the volume of plasma administered is critical.

HUMAN ERROR

The importance of the hazards associated with blood transfusion depends to some extent on human reliability. It is apparent that some may result from error on the part of the prescribing physician. However, a unit of blood delivered to the bedside has been exposed to a great many opportunities for human error. The acceptability of the donor must be judged, asepsis must be ensured throughout the processing program, blood-typing tests must be interpreted accurately, the products must be labeled appropriately, and the labels must be read and understood correctly. It is not just a handful of men at two or three manufacturing establishments who might make mistakes, but rather the blood collectors, laboratory personnel, and persons administering transfusions at well over 5000 collecting stations, blood banks, and hospitals. This circumstance makes it difficult to obtain accurate data on the frequency of error, but the problem of manning so many responsible positions with adequately trained and experienced personnel is obvious. Procedures for eliminating most of the hazards are known, but in the present arrangements for providing blood services it is not possible to ensure their universal application. In the interest of meeting the overriding need of the patient for blood products, it is sometimes necessary to accept risks of unknown magnitude. The physician's judgment would be greatly enhanced by a knowledge of the degree of risk with which he was confronted. Only by careful monitoring of transfusion activity can the incidence and severity of transfusion reactions be determined.

Blood Resources

The basic concept of blood-component therapy has been well stated by the American Association of Blood Banks:[1]

> Selective transfusion of appropriate blood components is preferable to the routine use of whole blood. The development of a system of plastic bags with integral tubing for collection, processing and storage, as well as recent advances in high-speed refrigerated centrifugation, are responsible for the availability of blood components. The physician can now select the component that is best suited to correct the patient's specific physiologic deficiency, thereby avoiding most of the hazards inherent in whole-blood use. The required fraction can be transfused in a concentrated form, achieving effective levels in the patient without overloading his circulation.

To determine the extent to which our blood resources are being used efficiently, it is necessary to examine first the nature of those resources and then the extent to which they are made available as components. Reliable data on the amounts of blood and plasma collected in the United States are not available. The Committee on Blood of the American Medical Association, in its 1969 *Directory of Blood Banking and Transfusion Facilities and Services*,[3] reports the results of a survey of activity in 1967. Although that report is the sole source of information concerning blood-service activity on the national level, lack of response from many facilities, obvious misinterpretations of the questionnaire, and suspected duplicate reporting of collections suggests that its data be treated only as a base. Requests for data were sent to 10,443 facilities assumed to have blood-banking or transfusion services, including members of the American Association of Blood Banks, the American Hospital Association, The American National Red Cross, and the American Osteopathic Hospital Association; 3383 (32%) failed to respond, and, of the 7060 that responded, 1435 reported having no blood-banking or transfusion services. Those responding reported drawing a total of 6,610,166 units of blood during 1967. In comparing these figures with those published by the Joint Blood Council in 1958, it is interesting to note that, although the number of facilities engaged in blood banking or in transfusion had increased by 150%, the amount of blood drawn had increased by only 46%. The fact that two-thirds of the blood drawn was reported as having been issued to other facilities emphasizes the extent to which using hospitals depend on collection and distribution of

blood by supplemental facilities; and 40% of the hospitals using blood reported no collecting activity.

There are no data at the national level to indicate the extent to which the amount of blood drawn meets community requirements. The AMA Directory suggests that 4.9 million of the 6.6 million units drawn were administered to patients as whole blood or red-cell preparations. One can neither infer that 4.9 million units represented the real needs of patients in terms of good clinical practice nor that that amount optimally met their stated needs. If a local shortage exists, a surgeon who prefers whole blood must frequently use plasma, albumin, or electrolyte solutions. It is possible, however, in view of the need for periodic community pleas for donors in situations of crisis or imbalance of stocks, to conclude that periodic shortages of blood at the community level jeopardize the lives of patients and cause the postponement of elective surgery.

With respect to the availability of plasma components, it is clear that commercial firms engaged in the processing of plasma into albumin or plasma-protein fraction are not able to meet the demand of the market. Federal regulations provide for a degree of relaxation of the procurement standards imposed on manufacturers when a biologic product is in "short supply." The Director, National Institutes of Health, has declared serum albumin, plasma-protein fraction, fibrinogen, antihemophilic factor, immune serum globulin, and six specific immune globulins to be in short supply. In particular, the quantities of antihemophilic factor concentrate now available represent only a very small fraction of the known clinical requirement.

The Blood-Service Complex

In a sense, there are four sectors of activity in the provision of blood services. The lines of demarcation between these sectors are not always clear for all activities, but they are clear where major roles are concerned. The population of the country, as one sector, may be thought of as consisting of blood users and blood donors. The second sector includes the health professionals (physicians and surgeons) who, because they translate the apparent needs of patients into "prescriptions" for blood or blood components, may be called the demand-effecting sector. The third sector comprises the persons, organizations, and facilities that collect blood from donors and process it into forms ultimately used in the treatment of patients. Finally, there is the sector, generally embracing hospitals, that actually administers blood and blood products to patients. One is tempted, for purposes of analysis, to refer to the over-all arrangement in which these sectors operate as a "system." But lack of system is so characteristic of the arrangement that it might better be called a "complex" (see Fig. 2).

Before World War II, there was little demand for transfusion, and only a few hospitals made an effort to maintain stocks of refrigerated blood to meet their own needs. By the end of the war, three major developments had occurred. Of greatest significance was the increased demand for blood by physicians and surgeons who returned from military service with a new respect for the therapeutic properties of blood. The second development was the standardization of the ACD anticoagulant-preservative. The third was the acquisition by the American National Red Cross of a great deal of experience in using its national organization for recruiting large numbers of donors and in handling the blood collected. As the demand for blood increased, more "blood banks" were created, many of them established by communities on a nonprofit basis to provide for the needs of their own hospitals. Competition for donors often arose between existing hospital blood services and community facilities and between community facilities and Red Cross collecting activities. Blood banks of a commercial nature appeared. The American Association of Blood Banks was established as a trade association and provided operating standards and a clearinghouse service for its members. Laboratory standards were prescribed by two agencies of the federal government and by some states and counties. A substantial industrial effort developed in the field

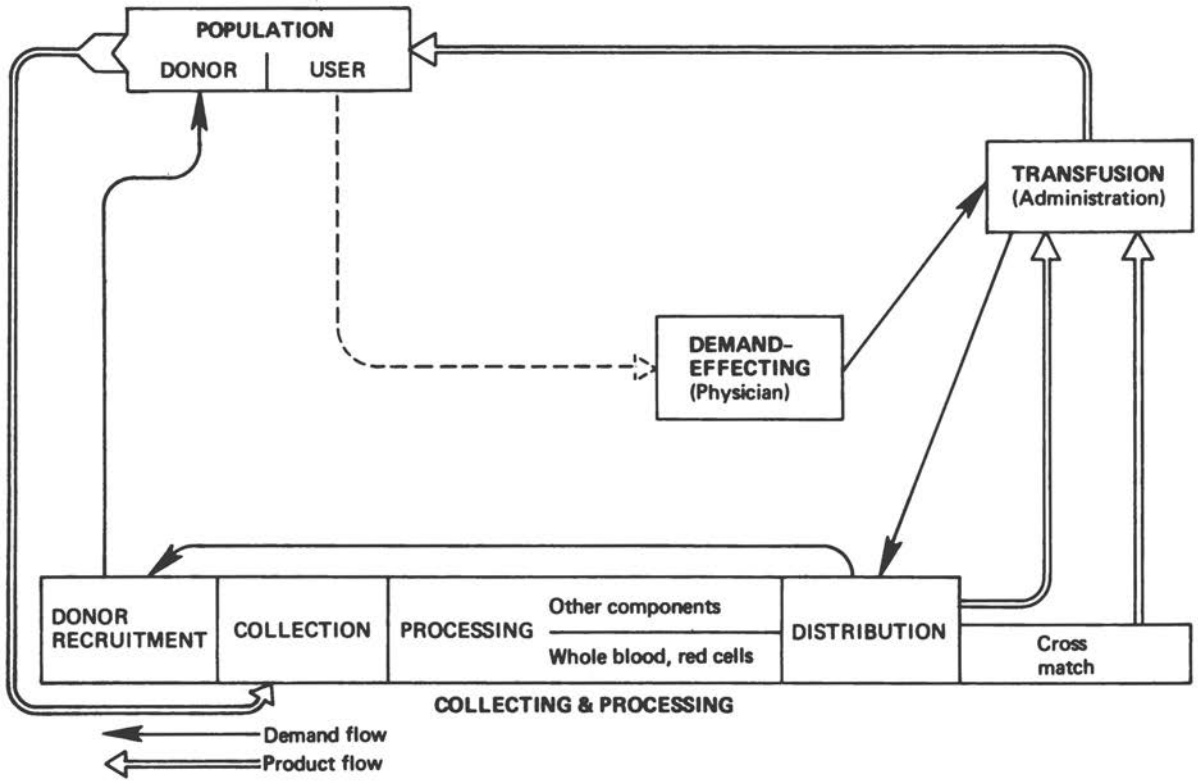

FIGURE 2. The blood-service complex.

of plasma fractionation, the preparation of blood-typing sera, and the manufacture of equipment for collecting and processing blood. For the most part, however, the center of blood-service activity remained at the community level. There was no point from which the total activity could be surveyed, coordination achieved, or direction and impetus given to efforts to improve the service. It is with this understanding that one should study the sectors of the current blood-service complex.

THE DEMAND-EFFECTING SECTOR

In examining the workings of the blood-service complex, it would appear logical to start with the patient, who is the source of the demand for blood. However, because the need of the patient has an effect only when it is expressed by the physician who is caring for him, we shall start with the health profession.

Whole blood is sometimes prescribed in circumstances in which good medical practice would suggest alternatives. A healthy adult can lose 1 liter of blood without serious effects, and the loss of 500 ml is inconsequential. It is generally agreed that there is no justification for the preparation of patients for surgery by routine transfusion solely to meet an arbitrary hematologic standard. But many transfusions are still prescribed for that reason. The infusion of red blood cells is necessary only when the oxygen-transport function of the blood is reduced, or is likely to be reduced, to unacceptable levels. In such circumstances, the manner in which the red cells are administered (whole blood versus red-cell preparations) has no effect on the demand for whole blood. There are, however, surgical and medical circumstances in which whole blood is being ordered but in which albumin or protein fractions, synthetic colloids, or electrolyte solutions would be equally effective or even preferable. Some 60%–80% of whole-blood transfusions should be replaced by the use of red-cell preparations—and possibly more. The attainment of such a usage policy would obviously make available a substantial supply of fresh plasma from which the various components could be extracted. However, the AMA Directory indicates that in 1967 only 12% of all units transfused were red-cell preparations. Current estimates of the nationwide use of red-cell preparations run from 5% to 20%. But in Massachusetts, the use of red-cell preparations, which constituted 14% of all transfusions in 1967, was increased to 23% in 1968 and 28% in 1969. And at one New York teaching hospital (Albert Einstein College of Medicine/Bronx Municipal Hospital Center), a usage of 80% has been attained.

It thus appears that a great deal of valuable plasma is being administered to patients who, in the light of current concepts of blood therapy, do not

need it. To some extent, this circumstance might be attributed to the fact that red-cell preparations are not always available to the prescribing physician. However, inasmuch as the blood services provided at a given facility generally reflect the preferences of the using physicians, it is probable that the apparently excessive use of whole blood is traceable largely to the physician population.

In many communities, the physician, even if he is aware of the benefits ascribed to component therapy, continues to regard whole blood in an almost mystical light and is reluctant to deny his patient any of its potential restorative powers. He may acknowledge that red-cell preparations alone can restore oxygen transport and that albumin alone can restore blood volume; but he still believes that the natural combination is best for his own patients. Neither the surgeon, with his attention focused on *his* patient undergoing surgery, nor the internist, dealing with *his* patient with anemia, is likely to be moved by economic considerations or by the need of other patients for products present in the plasma of the blood about to be transfused.

The concept of component therapy espoused by the American Medical Association in 1970 was considered sufficiently valid in 1963 to be included in the National Academy of Sciences publication, "General Principles of Blood Transfusion."[14] One reason why it had gained so little acceptance within the medical profession in general may be found in the physician's educational process. That process has three main components: formal medical education, continuing education by peers, and experience and circumstance. Most physicians now in practice were taught very little in medical school about the use of blood and have since acquired little knowledge of component therapy, primarily because the papers concerned with it have usually been directed at hematologists and those involved in blood banking. Interns and residents learn from the attending staffs of their hospitals; because the staffs are representative of the practitioners referred to above, there is little opportunity for house staffs to acquire familiarity with the concept of component therapy. It does not appear that the present generation of medical students will stimulate wider acceptance of the concept. The competition for curriculum hours and the trend away from required subjects in favor of early electives do not favor an attempt to teach component therapy to the student. In one eastern medical school last year, only 50% of the students were exposed to hematology, and the one scheduled period covering component therapy was canceled because of the visit of a distinguished lecturer.

In lieu of straightforward education, it has been demonstrated that a measure of control over access to blood products within a hospital can alter usage patterns. In a few hospitals, the director of the blood services is permitted in some circumstances to request justification of orders for whole blood, as opposed to red-cell preparations. In some cases, rules require that a specific

proportion of blood given to a single patient be in the form of red-cell preparations. This type of action, taken in the interest of conservation of blood as well as in patient welfare, may be construed by some as infringing on the privileges of the practitioner. However, it should be noted that, where it has been taken, a genuine acceptance of the concept of component therapy has ultimately been achieved.

One promising effort in the field of physician education is that being made by the American Association of Blood Banks with the support of the U.S. Public Health Service. The Association has for 3 years conducted, throughout the country, an excellent series of workshops on component therapy. However, because the instruction has been primarily at the technical level, the workshops have attracted few physicians. To reach the latter group, the Association has recently produced and distributed a "Physicians Handbook of Blood Component Therapy,"[1] which is complemented by an audiovisual lecture consisting of 109 slides and a 55-min audio tape. The Association has distributed 50,000 copies of the handbook and ordered a second printing of 25,000 copies. Copies have been distributed to (among others) the administrators of all hospitals registered with the American Hospital Association (with an endorsement by the director of that organization), members of the Association of Hospital Directors of Medical Education, directors of medical education at all medical schools, chairmen of state medical-society committees on blood, and pertinent professional journals; 160 sets of the audiovisual lecture have been shipped. It is interesting that two blood-bank supply firms have purchased nearly 1000 copies of the handbook for presentation to physicians by their detail men.

THE COLLECTING AND PROCESSING SECTOR

The collecting and processing sector of the blood-service complex is responsible for five basic operations: recruitment of donors, drawing of blood, identification and labeling of units of blood as to the results of blood-grouping and other tests, preparation of blood components, and ensuring compatibility of donor blood with recipient blood. In 60% of the hospitals in the United States, all five operations are carried out to some extent. Outside those hospitals, responsibility for the individual operations is distributed variously. Some agencies only recruit donors, and others only collect blood. Generally speaking, however, most blood is collected and initially processed by hospital blood banks, community blood services, and industrial-scale plasma processors. There are differences within those categories, such as the extent to which donors are paid and the degree to which profit is a motive, but for the most part, they are distinguished by the quantitative or geographic aspects of the clientele served.

Hospital Blood Banks

In 1967, 40% of the hospitals performing transfusions did not themselves collect blood from donors. The remaining 60% collected 23% of the total volume of blood drawn in the United States that year. The role of the hospital in blood collection appears to vary with geographic factors and the availability of nonhospital blood services. According to the AMA Directory, 73% of the hospitals in Montana, where there is only one nonhospital source of blood, met at least some of their own needs, whereas only 18% of the hospitals in California did so. A hospital blood bank frequently serves the community by lending blood or components to other hospitals and in turn relies to a varying extent on other blood-service operations within the community to meet its own needs. Donors are recruited through requirements for replacing blood given to specific patients, through calls for volunteers to replenish dwindling stocks, or through the inducement of a fee. A blood bank is normally an integral element of the hospital, with responsibility for its operation resting with the head of one of the clinical departments. The degree to which it participates in the economic support of the hospital varies widely.

One measure of the efficiency with which blood resources are used is the proportion of whole blood that becomes outdated or must be discarded for other reasons. This loss generally takes place within the hospital. The AMA Directory indicates that approximately 25% of the blood drawn in 1967 was not transfused either as whole blood or as red-cell preparations. From the data available, however, it is not possible to conclude that that amount of blood was wasted; but in a 1969 survey of laboratories and hospitals in the State of New York (exclusive of New York City),[13] it was determined that, although 63% of the blood collected was reported as "transfused" (37% therefore "not transfused"), only 20% was specifically reported as "discarded." In the same area, during a period of donor shortage (August 1969), 30% of the blood distributed to hospitals was returned to the community blood services unused and often too late for reissue.

From the perspective of the patient's bedside, a demand for blood arises when an attending physician prescribes whole blood or a blood component. From the perspective of a blood bank, a demand might arise when the level of blood stored against anticipated physician requests falls to a critical point. Because transfusion is so often required for surgical or medical emergencies, the ability of a blood bank to forecast demands accurately is rather limited. The difficulty is compounded by the fact that the forecast must include a qualitative as well as a quantitative judgment, in that the appropriate mix of ABO and Rh groups must be sought. The fact that refrigerated whole blood is not used after 21 days in storage and is more or less wasted if not used acts as a restraint on the normal tendency to overstock to be on the safe side.

This dilemma assumes its greatest magnitude in small hospitals, where demands for blood are infrequent but must be expected.

The 20% discard rate mentioned above is probably not exceptional where isolated small hospitals are concerned, and that has an obvious bearing on the demand for whole blood. Maximal utilization of collected whole blood can be approached only if the turnover of a blood bank's inventory is sufficiently rapid to preclude outdating; i.e., the patient population served must be large enough to produce demands not only for the volume on hand but, in particular, for all the specific blood groups represented in the inventory. That situation may be attained in a large, active metropolitan hospital complex; it may be approached within a reasonably compact array of independent hospitals served by a single blood-service facility; but it is rarely found in small isolated hospitals or in areas where regional facilities are established to serve such hospitals. The key to efficient use of blood is the maintenance of minimal inventories at using hospitals, which can be achieved only if adequate communication from the standpoints of exchanging requirements, inventories, and blood itself is available. In such circumstances, a hospital can rely on a blood-service facility to meet its emergency needs, and the service facility can redistribute unused blood to its other customers before it is outdated. For such an operation there must be a degree of formal organization, as well as standardization of blood processing, storage techniques, and reporting.

Community Blood Services

The characteristic feature of this type of operation is that it is designed to meet the needs of more than one hospital within a community or, frequently, within a region. Depending on the facilities and technical competence available, a community blood service may provide whole blood or specific blood products—red-cell preparations, frozen plasma, cryoprecipitate, etc. It may be established and operated on a voluntary basis by the community, as a private not-for-profit enterprise, as a private profit-making establishment, or by the American National Red Cross. In 1967, the first three types of activity accounted for 30% of the blood collected in the United States, and the 58 regional centers of the Red Cross accounted for 46%.

A small number of community blood services are members of some operating organization, in the sense that they are responsible to and under the supervision of some directorate. The largest of these organizations is the Blood Program of the American National Red Cross. It serves hospitals in 47 states and uses the resources of 1680 local Red Cross chapters. Typical of the nature of the Red Cross operation is the fact that, in 1969, 86% of the blood collected was collected by mobile units. Of the total collection, 53% was donated within the general community, 27% at industrial plants, 6% at educational

institutions, 6% by members of the armed forces, and 2% at prisons; 6% was from miscellaneous other sources. About 12% of the donations were for designated patients or other specific purposes. Although the central headquarters of the Blood Program prescribes techniques, equipment, and standards of operation for its collecting agencies, nonmedical administrative policies are to a great extent decentralized to the community level. Quotas, based on population density, are frequently prescribed.

The next most active organization in the blood collecting field is Blood Services (formerly Southwest Blood Banks), whose 25 banks, operating for the most part west of the Mississippi, collect and distribute approximately 20,000 units of blood per month. In 1967, it collected 3% of the national total. The member banks of Blood Services are sponsored by local county medical societies, which provide advisory groups. The organization is operated on a not-for-profit basis.

East of the Mississippi, the Interstate Blood Bank system maintains central facilities in four cities to which blood collected by some 20 centers is sent for processing and distribution. The system is said to collect approximately 10,000 units of blood per month. It is operated for profit.

One undertaking of the National Blood Resource Program[12] of the National Heart and Lung Institute is a series of studies to determine the feasibility of a computer-based inventory system for blood and blood products that might be applicable on a regional or even a national basis. The anticipated advantages of such a system are that it would make it possible to distribute existing supplies of blood and blood products more efficiently and rationally; to prevent or meet local shortages due to unpredictable fluctuations in supply and demand, by drawing on temporary surpluses elsewhere in a given region; and to redistribute local surpluses routinely, thereby reducing whole-blood losses due to outdating in storage.

Industrial-Scale Plasma Processors

Some commercial enterprises and a few public facilities procure plasma for large-scale production of blood components. They may contract simply to process plasma in the possession of other agencies, but the major output of the commercial enterprise finds its way to the marketplace. There are 13 establishments engaged in the large-scale processing of plasma. It is estimated that they processed a total of more than 800,000 liters of plasma in 1969. This plasma represented collections at plasmapheresis centers operated by the establishments themselves and purchases from other plasmapheresis or blood-collecting facilities. The relative contributions of these sources are not known, but plasmapheresis involving paid donors has probably become a major source of plasma for the commercial establishments.

In spite of the multitude of facilities that collect blood, separate red cells from plasma, and prepare some components on a limited scale, commercial producers of plasma products constitute the only source of albumin, immunoglobulins, AHF concentrate, and blood-typing sera in great volume, suitably packaged, standardized, and distributed through nationwide sales systems. This industry seeks to increase the number and the quality of therapeutic products obtained from plasma. Its basic problem is the market value of plasma components versus the cost of procuring and fractionating the plasma. In the process of deriving AHF concentrates from fresh-frozen plasma, albumin and gamma globulin are acquired. The market for gamma globulin has recently declined, so that the cost of fractionation must be recovered in the prices of albumin and AHF. The price of albumin, however, is fixed at that of the product obtained from the less expensive source of unfrozen or outdated plasma; hence, the price of AHF may well reach an unacceptable level. To counter that development, industry is expanding its effort in the field of of hyperimmune globulins in the hope that the value of the globulin fraction of plasma may once again help to defray a larger portion of the cost of fractionation.

In recent years, generally speaking, the period between the introduction of a new processing technique or a new blood product at the laboratory level and the adoption of the technique or the marketing of the product by industry has become extensive. For example, the anticoagulant-preservative ACD first appeared in the medical literature in December 1943. It was in use by the U.S. armed forces 16 months later. CPD, however, which promised an additional week of useful life for stored blood, was announced in 1961 and as yet is licensed only as an additive to whole blood for transfusion within 21 days, the plasma of which cannot be used for the preparation of immunoglobulins. This circumstance appears to be related, on the one hand, to the increased Congressional and popular concern with the hazard of therapeutic agents and the ethics of human experimentation and, on the other, to the realities of the marketplace.

In order to acquire a license to produce and market a new product or an "old" product prepared by a new technique or for a new use, the manufacturer must show that it meets "standards, designed to insure the continued safety, purity, and potency of such products, prescribed in regulations. . . ." These standards are prescribed by the Secretary of Health, Education, and Welfare. In the case of new products, the establishment of standards is not always easy. In some instances, there is a lack of experience or precedent. Often, the climate of public opinion requires that criteria for purity and safety be far more comprehensive than those established in the past. As a result, the potential manufacturer sometimes has difficulty obtaining from the regulatory agency sufficiently definitive standards to permit him to

embark on a testing program with any assurance. The review by the regulatory agency of the results of the tests originally agreed on is sometimes followed by requests for further testing—to answer questions not previously anticipated. A requirement for the demonstration of the safety and "potency" of a product when administered to man poses more of a problem to the manufacturer today than heretofore. Safety can be demonstrated in a healthy subject, but the potency of most products can be ascertained only by administration to patients. In both cases, testing must be carried out in conformance with codes and regulations that have become increasingly restrictive in the last decade. One aspect of this circumstance is the widely held concept that a substance that might involve a risk should be administered to a subject on a trial basis only if it may be expected to be of benefit to him. Another is the requirement that the subject give his "informed consent" to the procedure. The lack of agreement within the courts as well as within the scientific community on the criteria by which the subject may be considered "informed" has had a distinct inhibitory effect on many clinical investigators. In this regard, the Commission on Drug Safety in 1964 reported that:

> Drug safety in itself is not and cannot be the first consideration of the manufacturer, nor of the physician. The governing principle must be to provide the best possible therapy for the patient, and this means that the possible risk inherent in new compounds must be weighed against potential gains in efficacy. The seriousness of the illness, quite clearly, dictates the margin of allowable risk. If safety *per se* were the overriding factor, few compounds would reach the clinical test stage since the risk of the unknown would almost always cancel out the known risks associated with established therapeutic agents.[8]

The regulatory deterrents to the developer of a new product acquire greater importance in the light of economic factors. The market for blood products is small by today's industrial standards. There are only a limited number of patients who are potential users of a product—that number cannot be increased by any form of advertising campaign. In many instances, a new product simply replaces an old one. Its appearance does not generate a new market, nor is a more remunerative sales price often feasible. It is perhaps understandable that industrial producers of blood products are sometimes less than enthusiastic about committing their resources to the task of transforming a laboratory development into a licensed and marketable product. Some means should be sought of supporting and easing the task of developing new products.

Associations

There are two organizations which exist to further the aims of their constituent blood services. One has made significant contributions in the scientific and technical, as well as the operational, areas of blood therapy; the other

has a more restricted scope. The first, the American Association of Blood Banks (AABB) was established in 1947 as a trade association of local and regional blood banks. Its membership includes approximately 1200 hospital and other blood services. The AABB has established standards for its member banks and transfusion services and maintains a program of inspection and accreditation. It maintains a clearinghouse program involving 2800 hospitals that in 1969 permitted donors, through a credit system, to replace at their local collecting facilities some 250,000 units of blood given to patients in other cities and arranged for the actual transfer of approximately 120,000 units of surplus blood between facilities. The AABB provides to its members the services of 28 regional reference laboratories for serology studies and consultation and a rare donor file supported by 10 depots in which rare red cells are stored in the frozen state. Some medical technologists are trained and, in cooperation with the American Society of Clinical Pathologists, are certified by the Association.

Within the AABB, there are 10 times as many hospital blood banks as community blood services. Because the problems and concepts of the two groups are not always in accord, nine of the community services, including Blood Services, have established the Community Blood Bank Council. The aims of the Council are (1) to foster the establishment, growth, and quality of performance of community blood-bank services, (2) to collect, study, organize, and interpret information on administrative and operational activities of community blood banks, and (3) to provide, where possible, a counseling service and practical help and information to communities organizing or reorganizing comprehensive community blood programs. The organization appears to be oriented largely toward the economic aspects of blood services, rather than the scientific.

Regulation

The collection, processing, and distribution of blood in the United States are regulated by a variety of agencies. Federal interest is expressed with respect only to blood or blood products that are transported across state lines. Approximately 80% of the whole blood used in transfusion is obtained from facilities holding federal licenses for interstate shipment. The Division of Biologics Standards (DBS) is responsible for the inspection and licensing of banks and laboratories to prepare specific products. The Food and Drug Administration (FDA) regulates the nature and the quality of containers and equipment involved in blood banking. The Center for Disease Control (formerly National Communicable Disease Center) establishes standards for, inspects, and tests the proficiency of laboratories involved in cross-matching and blood processing for interstate operations. Coordination is not enhanced by the fact that these three agencies

operate, respectively, within the organizations of the National Institutes of Health, the Consumer Protection and Environmental Health Service, and the Health Service and Mental Health Administration. There are also various degrees of regulation at the state and local levels. The American Association of Blood Banks provides a voluntary inspection and accreditation service for its members; it is also available to nonmembers. The College of American Pathologists offers inspection, proficiency testing, and accreditation that is accepted by the Center for Disease Control (CDC) for its aforesaid licensing purposes.

Federal authority in the field of blood and blood products is far from clear-cut. The FDA accepts a responsibility under pertinent statutes by defining a container of blood as a "drug" because it contains a packaged anticoagulant agent. The DBS operates under the provisions of a 1902 statute, now Section 351 of the Public Health Service Act (42 USC 262), that does not mention blood for transfusion. It assumed its role by interpreting the term "therapeutic serum" to include blood and blood products. In 1968, the U.S. Court of Appeals, Fifth Circuit, held that whole blood and packed red cells were not biologic products within the meaning of Section 351 and were therefore not subject to regulation or control thereunder. The Court based its decision on the rationale that, at the time the predecessor of Section 351 was enacted, the product and processes involved in blood transfusion were unknown and therefore not within the intent of Congress.[6] In the face of this decision, the Secretary of Health, Education, and Welfare re-established some measure of authority by amending the good-practice regulations for drugs under the Federal Food, Drug, and Cosmetic Act to incorporate by reference the standards for manufacturing, processing, packaging, and holding blood and blood products that were issued under Section 351. Legislation now pending (H.R. 15961 and S. 3601) would establish this authority on a statutory basis by specifically adding to Section 351 the words "blood, blood component or derivative." The CDC carries out the statutory responsibility of the Secretary of Health, Education, and Welfare for regulating laboratories that, in interstate commerce, engage in the examination of "material derived from the human body" (42 USC 263a). It may exempt from its regulatory activities laboratories in states that have laws equal to or more stringent than its own and laboratories that have been accredited by the Joint Commission on Accreditation of Hospitals of the American Medical Association, the American Osteopathic Association, the College of American Pathologists, or any other national accreditation body approved by the Secretary.

Another regulatory agency asserted control over the distribution of blood and blood products in 1964. In that year, a Kansas City, Missouri, nonprofit community blood service, the local hospital association, and the hospitals and their pathologists were charged by the Federal Trade Commission (FTC) with

illegally combining to restrain interstate commerce in human whole blood by restricting two commercial blood banks (using paid donors) in Kansas City, Kansas. The charge stemmed essentially from the refusal of the respondents to accept for transfusion blood that had been collected by the two commercial banks. An FTC examiner decided against the defendants, and in 1966 the FTC upheld his decision. Two facets of this case are of interest. First, although both commercial banks were properly licensed by the DBS, the defendants allegedly had acted out of conviction that the blood in question was not of acceptable quality. That prompted the Chairman of the FTC to say that "a group of private citizens, no matter how public spirited or altruistically motivated, may not relegate to themselves the essentially governmental function of determining the standards which will be applied in the interstate operation of blood banks." Second, the FTC decision involved the ruling that human blood is a commodity or an article of commerce and thus subject to federal antitrust and fair-trade laws. On that score, the House of Delegates of the American Medical Association in 1967 (1) endorsed the concept that the procurement, processing, distribution, or use of human blood, and other human tissues is the rendering of medical services by all who participate therein, and does *not* constitute the selling of a commodity; (2) reaffirmed the position that, beyond assurances that all such participants shall exercise the highest standards of professional judgment and procedure, the results of medical services cannot be guaranteed; and (3) directed the Board of Trustees to support legislative action at the federal level to implement this concept and position and to urge the constituent medical societies to support similar action in their own jurisdictions.[5] Such legislation has been introduced periodically, without success, since 1967 and most recently (H.R. 13888) in September 1969. In January 1969, the U.S. Court of Appeals, Eighth Circuit, found that the FTC did not have jurisdiction over nonprofit organizations.[9] The FTC did not challenge the decision. In a somewhat related action, a New York court, in a case involving hepatitis transmitted by transfusion, recently found the hospital not liable for breach of warranties but refused to dismiss the case against the commercial blood bank involved. The court stated that "in the instant situation, we have solely a transfer of blood and no services are rendered by the blood bank to the hospital" and that "a blood bank is clearly a merchant with respect to goods of that kind and it appears that under the Uniform Commercial Code, this implied warranty of merchantability attaches to the sale of blood."[7]

Coordination and Direction

Most of the agencies with regulatory responsibilities related to the blood-service complex exercise principally a constraining function—they prescribe minimal standards and state what cannot be done. The only coordination of

effort possible in such circumstances is that which results from the establishment of standards for procedures and products. The existing regulatory agencies are not in a position to give direction to research and development, nor do they provide a particularly effective mechanism or even a forum by which the various elements of the blood-service complex can be brought together in the interest of promoting efficiency or of adopting higher than minimal standards.

However, some attempts have been made to promote coordination of activity within the blood-service complex. Upon its establishment in 1940, the Committee on Blood Transfusion of the National Research Council provided a forum in which the War Department, the Office of Civil Defense, the American National Red Cross, and later the Biologics Control Laboratory of the National Institutes of Health could exchange ideas with the scientific community, make decisions, and establish programs. In 1947, in the face of a rapid increase in the use of transfusion in civilian practice, the Red Cross met with the Board of Trustees of the American Medical Association to establish a "national blood program." The program was to be based on blood-collecting activities operated with the approval of county medical societies. In 1948, the AMA established a liaison committee to "coordinate medical work of the Red Cross." As the Red Cross began to establish local programs, those in some communities appeared to be in competition with established hospital blood banks. The latter had established positions within the community, frequently under the aegis of the local medical society, which provided access to donors to meet the needs of their own patients. The recruitment of donors and the services provided by the blood banks were closely oriented with clinical activities within the hospital. In most cases, the unique nature of the hospital-donor relationship was considered essential to its continued operation. The blood-collecting activities of the Red Cross, however, were directed to a greater extent at the less immediate needs of the community or region, rather than the patient or the individual hospital. The responsibility of the Red Cross ended with the delivery of blood to the hospital, whereas that of the hospital blood bank extended from donor recruitment through cross-matching often to the transfusion of the unit of blood. Because it was an extensive operation and its ability to recruit donors was enhanced by its historical humanitarian image and its widespread organization, the Red Cross program was viewed as a threat to the established role and status of hospital blood banks. In November 1947, partly to strengthen the position of the independent banks, the American Association of Blood Banks was established as a nonprofit trade association of blood banks and transfusion services.

In 1949, the AMA Committee on Blood Banks (formerly the liaison committee with the Red Cross) stated that:

there was urgent need for a national blood program capable of immediate expansion, that the Red Cross was the logical agency to assume responsibility for such a program and that steps should be taken to standardize equipment used in the program[and] recommended that [the AMA] cooperate with other agencies and conduct an education program toward the objectives of a coordinated program on the national level, with complete integration of private and hospital blood banks with the regional Red Cross blood centers on the local level, and an informed and trained medical profession.[2]

To arrive at some accommodation between the Red Cross and the AABB, a meeting of the Red Cross, the AABB, the American Medical Association, and the American Hospital Association was held in 1950. From that meeting came the "Boston agreement," which recognized the right of the Red Cross to establish community blood programs in peacetime without local medical-society approval, but required such approval in time of national emergency. With the coming of the Korean War, coordination of the collection of blood for federal agencies was vested in the Red Cross by executive order. In 1954, with the Red Cross operating 58 regional centers, the House of Delegates of the American Medical Association adopted a plan for a national program that was to include all the signatories of the "Boston agreement" and the American Society of Clinical Pathologists and that called for the establishment of the National Blood Foundation (later the Joint Blood Council) to coordinate the activities of the agencies represented. The Council, however, lacked the power to make and enforce decisions, and was dissolved in 1962. With the dissolution of the Council, the Committee on Blood (now the Committee on Transfusion and Transplantation) of the American Medical Association was re-established, primarily to maintain liaison among the various elements of the blood-service complex.

In 1951, President Truman directed the Office of Defense Mobilization to provide, within that Office, "a mechanism for the authoritative coordination of an integrated and effective program to meet the nation's requirements for blood, blood derivatives and related substances." Having activated a Subcommittee on Blood within his Health Resources Advisory Committee, the Director of the Office of Defense Mobilization then published a directive that established a National Blood Program. Although the mission of the Subcommittee on Blood did not encompass peacetime activities of the blood-service complex, the attempt to achieve coordination under emergency circumstances seems pertinent to this review. The directive recognized that "excellent programs designated to provide sufficient blood, blood derivatives, and plasma expanders to meet basic civilian, military, and civil defense needs are being developed by the American National Red Cross and affiliated blood banks, the Department of Defense, and the Federal Civil Defense Administration." It went on to state that:

Coordination of these programs for the duration of the national emergency is essential in order to meet the blood needs of the country without unnecessary duplication of

effort or conflict of interests. This can best be achieved by integrating the related blood programs operating or cooperating on a national scale into a single National Blood Program. Such a program is of prime importance to the agencies involved and of concern and interest to other organizations engaged in blood programs such as the American Medical Association, the American Hospital Association, and the American Association of Blood Banks.[10]

The desired coordination was to be achieved through the operation of the dictum that no agency participating in the Program would duplicate the efforts of another without prior agreement among the agencies involved and the Office of Defense Mobilization. Donor recruitment was to be carried out in the name of the National Program, and not that of a single agency. The American National Red Cross was established as "the blood collecting agency for the defense needs of the National Blood Program." A Committee on Blood and Related Problems, established by the National Research Council, was to provide guidance and act as a forum for participating agencies in matters of research related to blood, blood derivatives, and plasma expanders. In 1967, a revision of the original directive added the word "Emergency" to the title of the Program and relieved the American National Red Cross of its role as the sole collecting agency for the federal agencies. In 1957, there was established within the Program what is now the Interdepartmental Committee on National Blood Program Research, maintained by the Secretary of Defense, for the purpose of coordinating "federal agency funding and programing aspects for research and development projects relating to the National Emergency Blood Program so as to best support that program." It was, however, stated that that mission "should not be construed as control or direction of the research of any agency represented on this committee." There is little evidence that the Committee has been able to achieve coordination in any sense other than the exchange of information.

In 1966, Congress appropriated funds for the establishment of a National Blood Resource Program. The directorate, with a staff of three physicians, is a part of the organization of the National Heart and Lung Institute. The Program is a cooperative endeavor involving a number of institutes and divisions of NIH and other federal and nonfederal agencies concerned with the acquisition, processing, distribution, usage, or study of blood. The Program's stated major goals are (1) to survey the nation's blood resources and their utilization in terms of present and foreseeable needs, and (2) to meet a steadily accelerating demand for blood fractions without undue strains on these resources, through improvements in technology that will make possible the more efficient production, storage, and distribution of blood products. In pursuit of the latter goal, the Program is supporting studies in the automation of mass production of plasma and the cellular fractions of blood, the development of high-yield techniques for large-scale fractionation of plasma, the

extension of the storage life of whole blood and cellular fractions through improved additives and freezing techniques, and the feasibility of a computerized national or regional system for the daily inventory of blood and blood products.

Discussion

The Committee has gained the impression that many administrative barriers and competitive motivations have interfered with the full exploitation of the potential blood resources of the United States. That can be attributed in large part to historical background. The development of knowledge of the therapeutic use of different blood components derived largely from academic sources over a 30-year period beginning with World War II; blood banking from the standpoint of donor recruitment, collection techniques, and simple storage as whole blood, first applied in the United States at the Cook County Hospital in Chicago, was further developed by voluntary agencies, such as the Red Cross, and quasicommercial agencies, such as private blood banks; regulatory and control mechanisms derived largely from standards established by government agencies whose authority was based on federal regulations originally promulgated solely for vaccines and serums and, to a lesser extent, from standardization committees and approved agencies of diverse voluntary associations, such as the American College of Clinical Pathologists, the AABB—and some state medical societies. The lack of coordination stemming from this multipronged development of blood use, blood research, and blood regulation was compounded by economic factors that made it profitable for commercial pharmaceutical firms to collect whole blood, fractionate plasma, and discard red cells, while hospitals a few blocks away were collecting whole blood, administering red cells, and discarding plasma. Such failure to integrate collection and delivery systems of this important biologic product were tolerable only until the supply became critical because of increasing needs.

Another influence preventing maximal utilization of blood components has been the innate self-interests that have inevitably developed in the diverse agencies and groups collecting and distributing blood. All too frequently, situations have occurred wherein the availability and distribution of blood and blood products in different regions of the country have depended more on the desire of agencies to strengthen their public image or enhance their competitive position than on the true needs of the community.

Given the foregoing circumstances, one is almost inevitably led to consider the possible impact of a federal or quasifederal agency with a broad mission of ensuring the optimal collection, distribution, and utilization of blood and blood products. Such an agency would transect historical relationships and impinge on the vested interests of the many private and public agencies now

functioning in this field. Some of the predictable responses to proposals for the orderly development of an integrated national blood program are discussed in the following paragraphs.

Agencies currently engaged primarily in whole-blood collection and distribution—the Red Cross, the AABB, and private hospital blood banks—would react to the necessity of merging their individual identities with an agency serving the larger needs of the nation. The requirement to integrate their blood-collection resources might be viewed unfavorably in terms of individual objectives. In this respect, a national program, to be effective, should preserve the operational integrity and spirit of such organizations but at the same time preclude the kind of competition that, from the standpoint of blood as a valuable national resource, leads to inequities and inefficiencies in procurement, distribution, and utilization.

Commercial corporations engaged in the preparation and distribution of blood products may feel threatened by the burden of further administrative processes. It is hoped that this fear would be more than balanced by the promise that regulatory processes would become more responsive to the broader public need.

Government agencies now charged with responsibilities in the blood-service field might be expected to respond defensively to any suggestion that they are not now serving the public interest to the fullest extent. Generally speaking, regulatory agencies should be in the forefront of the effort to adapt innovations in their fields to the public welfare. It is recognized that regulatory agencies operating in the field of human therapy may be forced by statute or by public opinion to give a larger measure of consideration to hazard than do other regulatory agencies in the government. As a result, regulatory activity with respect to blood and blood products has followed far behind the scientific discourse in the field, and the application of new knowledge in behalf of the broader public welfare has been considerably impeded.

The portion of the scientific community interested primarily in the acquisition of new knowledge may feel that the coordinating effect of a broader national blood program will restrict their freedom of research. One of the principal functions of such a program should be to seek out and encourage, with the broad national requirement in mind, appropriate funding for both nondirected basic research and directed applied research, regardless of the sector in which it is to be performed. The National Blood Resource Program was created within the National Heart and Lung Institute as an effort to provide that function. Although it has broad long-range goals and constitutes a valuable asset, it cannot, with its present resources and position in the structure, realistically influence the major organizational research goals.

Organized medicine and its professional societies, hospitals, and other health-care agencies will react to what may appear to be direction of medical

practice. They have experienced similar pressures and have shown themselves able to adapt once ultimate benefits are made apparent. Appropriately represented within a newly formed national agency, these groups may be expected to become a leading force in implementing advances in the field.

THE POPULATION OF USERS AND DONORS

The Users of Blood

Most people in the United States are potential users of blood products in the form of the specific immune globulins administered to prevent or attenuate the symptoms of such diseases as mumps, measles, and whooping cough. Fewer have need of whole blood, red-cell preparations, albumin, and other components and fractions of blood. Whole blood and red-cell preparations are usually administered to replace blood lost in the course of surgical procedures or accidental trauma or to correct anemia due to other causes. Some patients make heavy demands on local blood resources. Extracorporeal circulation in open-heart surgery may require 10 or more units of blood or red-cell preparations. Severe trauma, as in war wounds, has required as many as 100 units of whole blood. Many hemophiliacs require, annually, the antihemophilic factor from 300–500 units of blood.

There are a variety of types of blood-service operations, and a patient who receives a transfusion of blood or red cells may be expected to "pay" for it in a variety of ways (Table 1). In most blood-service facilities, recruitment of donors is the most critical problem. Therefore, the most widespread procedure is to ask the patient to "pay" by arranging for the replacement of the blood that was used for him and to add a service charge to his bill. Generally speaking, the monetary value of a unit of whole blood is based on the costs of recruiting and examining donors, the costs of collecting, testing, labeling, storing, and delivering the blood, and the operating overhead of the facility. These are the basis of the "processing fee." Within the hospital, the patient may be further charged for blood typing and the cross-matching of his blood with that of the donor and for the actual procedure of transfusion. If the hospital operates on the replacement system, the patient is usually charged a "replacement fee," which is canceled if he provides the necessary replacement donor(s). As an inducement to arrange for donors rather than pay the fee, the fee is frequently fixed at a high figure. To compensate for losses due to unsuitability or outdating, the hospital may ask that two or three donations be provided for the first unit of blood given the patient. The Blood Services organization uses a replacement fee of approximately $10, which is related to the cost of recruiting an acceptable donor. The average figure

TABLE 1 Transfusion Costs, Chicago, Ill., 1968 (in dollars)[a]

Hospital	Blood Service[b]	Laboratory Charge: Typing[c]	Laboratory Charge: Cross Match	Laboratory Charge: Other Svc.	Infusion	Total	Blood Replacement Policy and Value of Each Donor[d]
A	35.00	5.00	5.00	–	10.00	55.00	2 D each U on 1st 3 U (D=12.50) 1 D each U after (D=25.00)
B	25.00	3.50	7.00	–	12.00	47.50	2½ D each U (D=10.00)
C	28.00	3.50[e]	7.00[e]	–	15.00	43.00	1 D each U requested (D=14.00) Unlimited D accepted at 14.00 each
D	28.00	5.00	6.00	–	10.00	49.00	2 D each U (D=14.00)
E	28.00	3.50	7.00	–	12.50	51.00	1 D each U requested (D=14.00) Unlimited D accepted at 14.00 each
F	30.00	5.00	6.00	–	10.00	51.00	3 D each U (D=10.00)
G	28.00	7.00	7.50		12.50	55.00	2 D each U (D=14.00)
H (Rh-pos.)	30.00	–	–	20.00	–	50.00	In Hosp.: 1 D each U (D=30.00) Clearing House Credits = 15.00 each
H (Rh-neg.)	30.00	–	–	25.00	–	55.00	
I	30.00	5.00	8.00	12.00	12.00	67.00	1 D each U (D=30.00)
J (Rh-pos.)	30.00	5.00	13.00	–	5.00	53.00	2 D each U (D=15.00)
J (Rh-neg.)	35.00	5.00	13.00	–	5.00	58.00	
K	35.00	7.50	6.00	18.00	–	66.50	In Hosp.: 2 D each U on 1st 4 U (D=17.50) 1 D each U after (D=35.00) Clearing House Credits = 15.00 each
L	35:00	4.00	2.00	–	10.00	51.00	2 D each U (D=14.00) Patient pays 7.00 extra on each U
M	28.00	7.00	11.00	–	5.00	51.00	2 D each U (D=14.00) Patient pays 5.00 extra on each U to pay infusion fee
N (Rh-pos.)	25.00	4.00	5.00		6.00	40.00	2 D each U on 1st 3 U (D=12.50) 1 D each U after (D=25.00) on Rh pos.
N (Rh-neg.)	37.50	4.00	5.00	-	6.00	52.50	2 D each U on 1st 3 U (D=18.75) 1 D each U after (D=37.50) on Rh neg.
O	40.00	6.00[e]	4.00[e]	17.00	–	57.00	2 D each U on 1st 2 U (D=20.00) 1 D each U after (D=40.00)
P	40.00	10.00		–	15.00	65.00	2 D each U (D=14.00)
Q	45.00	16.00		–	12.00	73.00	3 D each U (D=15.00)
R (Rh-pos.)	50.00	10.00		–	18.75	78.75	2 D each U (D=14.00)
R (Rh-neg.)	60.00	10.00		–	18.75	88.75	

[a] Based on a survey by Mrs. Carol Grabowski, Donor Recruitment Administrator, Michael Reese Research Foundation.
[b] Includes blood procurement and processing, which are only occasionally billed separately.
[c] ABO and Rh.
[d] D = donor; U = unit of blood.
[e] Not charged if blood is used.

throughout the United States, however, is probably $25. In some cases, where the hospital has ready access to volunteer donors from the community or to paid donors, less importance is attached to the need for the patient to arrange for replacement donors, and cash settlement is more frequent. Some hospitals eliminate the entire service charge if additional donors are supplied. A patient who requires repeated transfusions over a long period poses a problem for a local blood-service facility because he develops new blood-group antibodies that make the search for a compatible donor increasingly difficult, and the service charge for such a patient or for any patient with a rare blood type may be very high.

The AABB has undertaken a survey of blood-bank fees and replacement policies. Initial returns indicate a rather wide range of fees throughout the United States. However, when these charges are considered in relation to the volume of blood collected by the reporting facility, preliminary studies indicate that the average fees for the majority of patients are about as follows:

	average
processing fee	$11.75
typing and cross-matching fee	13.50
infusion fee	6.75
donor replacement fee	24.50

The provision of or payment for blood is increasingly handled by third parties. Blood "assurance programs" are available to members of various organizations and industrial establishments or on a community or regional basis. In general, the arrangement is that 20 donations per year per 100 eligible members of the group will ensure that the blood needs of the entire group will be met. Some programs provide coverage for individuals and families for either the donation of a single unit of blood or the payment of a fee of $7.50–$10.00. It should be noted that, except for the Red Cross, these programs rarely accept the persons who most desperately need such coverage—those with hemophilia, leukemia, or aplastic anemia.

Major hospitalization-insurance carriers generally cover all costs related to transfusion. In the case of Medicare, the cost of the first three units of blood or red-cell preparations is excluded as a benefit. In the first 18 months of operation of Medicare, its beneficiaries arranged for the replacement of only about 25% of the blood administered to them, choosing, or being forced by lack of donors, to pay for the remainder. Insurance companies have frequently been reluctant to pay a high replacement fee for a transfused unit when they are aware that a unit of blood may be purchased, from a facility using paid donors, for as little as $20.00.

The Donors of Blood

In general, the qualifications for the donation of blood are that the donor be between the ages of 18 and 65 years, free of a disease transmissible by blood transfusion, and without a history of particular chronic disease. In the United States, there are well over 100 million persons in that age group. It is estimated that fewer than 10% of them are, on any given day, disqualified by reason of disease. A qualified donor may give blood as frequently as every 2 months, up to five times a year. This suggests that our potential resource is 450 million units of blood per annum. Yet, in 1969, probably no more than 7 million units of blood were donated, and many donors gave more than one unit each.

It is estimated that 2.5–3 million persons in the United States donate blood every year. The motivation of many is clear; they may (1) respond to a demand for the replacement of blood given to a specific patient; (2) participate in a "blood assurance" program, which demands regular blood contributions to guarantee the provision of blood when needed by a family member; or (3) be attracted by the cash payment offered by some blood-service facilities. All the donors represented in those three categories may be considered "paid" donors, because there is a fairly tangible reward for the donation. Accurate data are not available on the total number of such donors, but they are responsible for the success of many blood programs. The motivations of those who donate blood with no expectation of any type of payment are less clear. Certainly, some are responding to motives of altruism. Others may be responding to motives of patriotism, as in the donation of blood for support of the armed forces in Vietnam. Another group may be touched by a specific appeal for blood made on the radio or television. Still another may be responding to the social pressures placed on them by their peers, or simply to a challenge. This "pure volunteer" donor probably represents the largest proportion of the entire donor population. Unfortunately, there are no data concerning the extent to which the various categories contribute to our blood resources, nor do any definitive studies focus on donor motivations.

Lacking a complete understanding of the factors that draw a donor to a collection station, one may at least look at some of the problems that tend to inhibit the free flow of donors within the collection process. Assuming that the potential donor has overcome any distaste he may have felt for the process of donating blood, he must then appear at a collection site at an appropriate time. That usually means a sacrifice of time from his schedule and some effort in traveling to the site. When large numbers of donors can be assembled at one place, such as a school or industrial plant, the use of a mobile collecting unit minimizes, but does not eliminate, inconveniences for the donor. To

some extent, proximity to the donor population is sought by blood-service facilities that depend on paid donors, and their collecting centers may be found in urban areas where a concentration of people in need of ready cash may be expected. In the present system, however, about 20% of blood collection takes place on the premises of hospitals, with the problems attendant on travel to and from the collection site.

Almost every blood bank can point to the need for large amounts of blood to meet the increased numbers of accidents associated with national holidays, whereas the exodus of city dwellers during those periods results in the smallest numbers of collections. Except for the need for "rare" bloods, the optimal form of access to donors would be one in which donors of known blood types could be called on as needed. Generally speaking, a regular daily flow of untyped donors may result in an excess of units of blood of a given type. Irregular collection from large numbers of donors may, in addition, result in an excess volume of blood at particular times. One difficulty arises from the fact that a large percentage of all donors are donating for the first time, and few blood banks are willing to risk alienating potential donors by declining an offer on the grounds that a particular blood type is not needed right away.

Approximately 15% of the whole blood and most of the plasma obtained by plasmapheresis are collected from paid donors. In some instances, the blood of paid donors has acquired particular value because of an unusual blood group or a high yield of specific immunoglobulins. In general, however, the donor simply wishes to acquire cash in return for his blood. Blood-service facilities that pay for blood collected and sell it to hospitals or processing facilities are commonly referred to as "commercial blood banks." They appear to be somewhat suspect in the eyes of the remainder of the blood-service community. First, their ability to provide blood quickly and inexpensively has tended to lessen the degree of coercion that might be exerted by hospital and other community blood services on potential volunteer donors, particularly in the replacement type of operation. Second, there is some evidence that blood from paid donors generally carries a higher risk of transmitting hepatitis than does that from unpaid donors.

The latter circumstance needs further investigation. One recent study of 110 patients undergoing open-heart surgery, which usually required 20 units of blood less than 48 hr old, found that hepatitis occurred in 51% of the patients who received blood from paid donors but in none who received blood from unpaid donors. As opposed to an accepted incidence of less than one case of icteric hepatitis per 1000 units of "volunteer" blood transfused, figures ranging from 1.4 to 13.7 cases per 1000 units of "commercial" blood have been reported. From the standpoint of screening donors for the presence of hepatitis, the report of the Hepatitis Surveillance Program of the National Communicable Disease Center is of interest:

For serum hepatitis, the bulk of reported cases were from the 15 to 29 age group. Of the total number of patients with serum hepatitis, approximately 40 percent had received transfusions of blood or blood products in the 6 months before their disease. However, in the 10 to 19 and 20 to 29 age groups, only 7.5 percent and 14.6 percent respectively reported such a history of prior transfusions. A significant percentage of serum hepatitis patients from these age groups admitted to the parenteral inoculation of narcotics. Thus, it appears that, among patients with diagnosed serum hepatitis in this age group, parenteral inoculations may play a substantial role in the transmission of infection. For serum hepatitis cases among other age groups, the overwhelming majority of cases appear to be transfusion-associated.[11]

Although work on the hepatitis-associated antigen holds promise for detecting a large proportion of hepatitis carriers in the donor population, procedures currently used in selecting and screening donors must, in the near future, continue to be the key to control of transmission of the disease. At present, there is little more to go on than the information concerning his health and his habits that the prospective donor is willing to provide. A history of liver disease or jaundice or the taking of drugs by injection is sufficient grounds for the rejection of a donor. However, one is forced to suspect that a person who is reduced to such straits that he must sell his blood to supplement his income not only is more likely to have such a history, but might well be willing to suppress it. That reasoning, coupled with the hepatitis incidence rates cited above, has caused much of the blood-service community to equate the paid donor in the United States, and thus the "commercial blood bank," with a less trustworthy quality of blood.

THE TRANSFUSION SECTOR

The transfusion sector of the blood-service complex is the element that actually administers blood and blood components to patients. It warrants isolation from the other sectors on a functional basis, because it neither makes the decision to use blood nor is responsible for its processing. Thus, it is not of great significance in an analysis of the total blood-service complex. Its particular importance is related to the hazard of blood transfusion. It is in the transfusion sector that special effort must be made to ensure that a patient receives the unit of blood delivered from the laboratory for him and that the blood is infused at an appropriate rate. It is also in this sector that reactions to transfusion must be recognized and treated.

Conclusions

1. Human blood can no longer be viewed simply as a substance that is transferred from the vessels of one person to those of another. In current medical practice, human blood not only is required in the volume-for-volume replacement of whole blood lost, but with modern advances in clinical practice and laboratory techniques has assumed some of the characteristics of a raw material from which many therapeutic products can be derived. These products, if they are to be made available to all patients who need them, must be produced in sufficient quantity and placed in an efficient distribution system. When one considers these requirements in the light of the fact that the raw material can be procured only from human volunteers, it seems important to consider blood as a national resource that should be carefully managed.

2. The administration of human blood and its products, like the administration of many other agents, is accompanied by significant risks to the patient, many of which are avoidable. Coordinated efforts in the field of professional education and research, as well as in regulation, are required to minimize these risks.

3. Data presently available do not permit accurate assessment of the utilization of U.S. blood resources. There is a need not only for a comprehensive survey of the collection, processing, and distribution of blood and its products, but for a mechanism by which such activities can be continuously monitored.

4. Insofar as supply and demand are concerned, the nation's blood resources must be considered in terms of the need for whole blood and red-cell preparations on the one hand and the need for platelets and plasma fractions on the other. With respect to whole blood and red-cell preparations, there is evidence that whatever shortages occur are local and transient, or seasonal. Although these local shortages may well jeopardize the lives of individual patients and cause the postponement of elective surgery, one may conclude that the overall supply of whole blood and red-cell preparations is sufficient to meet present demands. As for plasma fractions, there is evidence of a shortage of such products as albumin, plasma-protein fraction, antihemophilic factor, and the specific immunoglobulins. These shortages are associated with two factors that should be of concern: the needs of many hemophiliacs are met only by extraordinary effort and expense, and there appears to be a substantial patient population that, if afforded the benefits of modern therapy, would signifi-

cantly increase the demand for plasma products. There is, therefore, an immediate need to increase the supply of plasma products and to anticipate an ever-increasing demand for such products.

5. The blood that *is* collected does not appear to be used efficiently:

a. A unit of whole blood administered as such is of benefit to but one patient. A unit of whole blood separated into its cellular and liquid componets is of potential benefit to a number of patients.

b. Whole blood is administered to patients for clinical conditions in which it is not necessary or could be replaced by solutions of electrolytes or colloids. It is administered to patients for conditions in which red-cell preparations would be preferable. Such usage results in the "waste" of fresh plasma from which a number of critical components could be prepared. An effort must be made to increase the acceptance, by those in the medical profession who prescribe blood, of the rationale for and benefits of red-cell preparations versus whole blood.

c. The full potential of a significant volume of whole blood that is collected is lost, because it is permitted to go out of date or is collected at small facilities that lack the means of processing it into components. There is a need for the more widespread development of regional arrangements by which a greater amount of blood can be separated into components and by which whole blood itself can be redistributed for use before it is outdated.

d. Fractionation of plasma by the single process now in use yields only approximately half the albumin, gamma globulin, and antihemophilic factor present in the original material. New processing techniques offering higher yields have been developed on a laboratory scale. The adaptation of these techniques to industrial application should be encouraged.

6. The federal regulatory agencies, by virtue of their limited missions and their limited resources, do not provide the type of regulation and standardization required to permit the free interchange of the national blood resources. State and county agencies frequently exercise their own regulatory functions. The American Medical Association, the American Association of Blood Banks, the American National Red Cross, the American Society of Clinical Pathologists, and the College of American Pathologists have all made contributions to the improvement of blood services through standardization, surveillance, training, and the promotion of cooperation. Their task is made difficult by the divergence of their interests, their lack of authority, and the absence of a unifying structure within which their efforts might be far more productive.

7. The lack of uniformity, within many areas, of the value ascribed to a unit of blood, or a product thereof, *as it is administered* makes it difficult to provide some patient groups with a rational explanation of the costs involved. The lack of uniformity of the value, be it money or "blood credit," ascribed to a unit of blood *as it is donated* appears to have an effect on the character

of the donor population and its readiness to donate. Some measure of uniformity in the method of arriving at these values should be sought. Particularly needed is a study of the effect of the practice of paying a donor, and the related practice of purchasing blood "coverage," on the nature and availability of the donor population.

8. There is no point within the federal government from which the blood-service complex is viewed in its entirety. There is a need for the establishment within or at the level of the federal government of an agency that, with the broad mission of monitoring the utilization of the nation's blood resources, can effectively channel the expertise, energy, and interest now isolated in individual professional organizations, government agencies, and pharmaceutical establishments into the task of making blood therapy a more readily available component of the total health service. This body must be in a position to:

a. Restrict the operation of blood services that are not economical, and further the development of systematized community or regional blood services.

b. Establish and monitor technical standards of operation.

c. Promote professional policies governing the clinical application of blood and blood products.

d. Establish unified policies of donor recruitment to the extent practicable.

e. Establish criteria for the determination of the monetary value of blood and blood products.

f. Establish criteria for the determination of the "credit value" of a unit of donated blood.

g. Give direction to the basic and developmental research on blood, blood products, and blood-service operations that is supported by federal funds, and seek to minimize the inhibiting effect of protective regulations on the application of the benefits of such research to the public welfare.

Recommendations

1. Blood should be looked on as a national resource, and its collection, processing, distribution, and use should be managed systematically. An agency should be established at the national level and charged with responsibility for all the functions necessary to the effective utilization of this resource. The determination of the precise nature of such an agency should await returns from various information-gathering studies (recommended below).

2. Current programs aimed at gaining wider acceptance of the principles of component therapy should be continued and expanded. However, it is necessary to point out that, as the demand for blood components increases, steps must be taken to ensure an adequate supply.

3. Steps should be taken immediately to acquire the information necessary to the development of specific recommendations for the improved management of the nation's blood resources. To this end, a number of studies and surveys are proposed in the appendix to this report. Several agencies and organizations are well situated to execute some of these. However, it is unlikely that the entire program can receive the desired impetus or be carried out effectively in the absence of some central source of initiative, coordination, and material support. In view of the stated aims of the Component Therapy Institute, it seems particularly appropriate for the Institute to assume this role.

Appendix: Studies that Should be Undertaken

OPERATION OF THE PRESENT BLOOD-SERVICE COMPLEX

National Survey of the Blood-Service Complex

The desirability of a study of the entire blood-service complex of the United States seems obvious. There is some information about large segments of the complex, but there is less about the smaller elements of the complex and none about the interactions among various parts of the complex. A study of the entire complex would seek data concerning the state of the system as a whole, donor functions, distribution functions, inventory functions, blood-component technology and processing, administrative and financing functions, and medical-usage functions. Other factors can be added—research capabilities, computer availability and use, etc.—but the functions listed above seem most necessary to an adequate assessment of our national resources. One major result of such a study should be the ability to project future needs and capabilities on a geographic basis.

National Survey of Legislation and Practices Concerning Blood

There seems to be little national legislation concerning blood usage. No systematic study could be found, however, of the legislation and practices that might govern blood usage at the state level, at the hospital level, or even at the county medical-society level. Such a survey, covering all aspects of blood usage, seems necessary for planning. Adaptation of a computer retrieval system such as is now used by the University of Pittsburgh for the storage and analysis of medical legislation would be the best way in which to handle such a project. One obvious benefit of such a study would be the ability to suggest uniform legislation and standard practices to permit and encourage the fullest utilization of our blood resources.

In-Depth Study of the Blood Component Therapy Program at Medical Installations of Various Sizes

Several major medical institutions are already extensively engaged in component therapy and have developed data-collection methods to assist in the

efficient use of blood. Included among the data collected are those related to the efficiency of the donor system, utilization of components by physicians of various specialties, processing costs to the institution, distribution problems and solutions, and hospital control of the blood service. Such data do not exist for smaller components of the health-care system. This suggestion envisages a study in depth of medical installations of various sizes, based on the data already obtainable from some large institutions.

Assessment of Medical Usage of Blood and Its Components

This study would entail a sampling of physicians, on a national basis, regarding their current familiarity with and application of component therapy, combined with a survey of physicians and surgeons who are engaged in the expansion of the therapeutic potential of blood components. It would permit projections of the extent of education needed and an assessment of potential new uses for blood components. Such an assessment, once made, can be used at regular intervals to monitor changes in the system.

Survey of Patients Requiring Large Amounts of Blood or Blood Components

Some types of patients—such as hemophiliacs, those with particular types of anemia, and open-heart surgery patients—typically require large amounts of blood or blood components. Some rough assessments of the distribution and numbers of hemophiliacs within a few large cities have been made, but there are no data on other types of patients, or for the nation as a whole. It is desirable, in assessing the nation's needs for blood and blood components, to include a special assessment of the size and distribution of the population of patients who, as individuals, make heavy demands on local resources.

MODERNIZATION OF THE BLOOD-SERVICE COMPLEX

Studies Related to the General Population of the United States

Knowledge and Attitude Studies There is obviously wide variation among the general population regarding knowledge of the clinical uses of blood and blood components and in attitudes toward the donation of blood. Although some small studies have attempted to look at this variation, none has developed norms for the population as a whole, nor made the obvious categorizations of knowledge and attitudes by age, sex, education, and socioeconomic conditions. Such a study can be made using the resources of one of the major surveying firms.

Study of Blood Donors Several blood banks in the United States have developed "stable" donor populations—i.e., persons who donate blood on a regular basis. It seems useful to study in depth one or more of these populations, to determine its motivations for continuing donor efforts. The object of such a study will be to develop approaches to increasing the donor population.

Studies Related to the Blood-Service Operation

Studies of the Effectiveness of the Blood-Service Operation As the demands for blood and for component processing rise, we shall be forced to make use of the most efficient systems we can develop. Thus, it is advisable now to look into the effectiveness of particular parts of the present health-care system. Studies related to the economics of blood collection in the major types of blood services, the wastage of blood, the distribution system, the proper utilization of personnel, the training of personnel, for example, are essential to the development of new models. Such studies must be made on a long-term basis, with consideration of appropriate size of region and geographic distribution.

Experimental Study of New Systems The studies of parts of the system should yield information that will permit the development of new models for effective blood collection and utilization. It would be well to test these new models on a small scale before attempting to apply them to large portions of the system. A series of small experimental studies applied to small geographic areas and to hospitals of various sizes could test the effectiveness of new models.

In-Depth Study of Effective Blood Services The several studies done under the aegis of the National Blood Resource Program and other agencies are a good beginning for an analysis of effective blood services. However, other studies remain to be done if we are to collect the type of data necessary to make planned changes in the system. For example, blood banking requires trained personnel at various levels. What kinds of training are required? What are the most effective ways to obtain such training? What licensing requirements ought to be applied? All these questions need answers, which can best be obtained from careful study of effective blood-service operations. Additional information needs to be elicited regarding organization of the blood service, technical handling of blood, economics of successful blood banking, and the distribution system. These aspects can well be studied by looking carefully at successful blood-collection systems of various sizes.

Studies Related to Health-Care Facilities

Studies of Blood Use within the Hospital Setting We do not have national data on the use of blood components within hospitals. We cannot say how many hospitals make efficient use of their blood resources and how many do not. We do not know how many hospitals have complete hematology laboratories and how many make use of outside commercial laboratories. Answers to these and other questions related to the blood resources of the nation seem to be necessary if we are to plan for the future. A national survey of hospitals, attempting to answer questions related to their use of blood resources, seems indicated.

In-Depth Studies of Hospitals Having Effective Blood Programs A number of medical centers have done an excellent job of moving from whole-blood usage to relatively routine usage of components. A series of in-depth studies of such hospitals is desirable. What strategies proved most successful? What arguments had to be used with different kinds of hospital personnel? What kinds of training programs had to be instituted? What kinds of efforts have gone into maintaining the progress that was made? Such questions can be answered only through an in-depth study of hospitals that seem to have made successful changes toward routine component therapy. There should also be a study of some of the hospitals that tried and failed to institute successful component therapy programs. Isolating both favorable and unfavorable factors may allow for the development of successful models.

Experimental Programs on the Introduction of Innovation During the next several years, it is to be expected that new techniques in blood therapy will be developed. In past years, the American health-care system has never been able to introduce new techniques systematically. Rather, an idea has been developed, and the physician or laboratory technician attached to a particular hospital has tried out the idea in his own setting. From there, it has diffused gradually to other medical-care facilities, sometimes rapidly, sometimes slowly, but almost always without direction. The establishment of a national system of "experimental hospitals" in which new techniques of blood component use can be tried and evaluated would seem extremely advantageous in developing the mechanics of change.

Knowledge and Attitude Studies within the Hospital Staff The success of any complete blood-resource program depends at least in part on the enthusiasm of the hospital staff. Just as we may expect to find significant attitude varia-

tion within a general population or within the donor population, we may also expect to find significant differences within the hospital staff regarding the use of blood. It seems desirable to assess these variations and attempt to relate them to successful or unsuccessful blood-resource programs.

Studies Related to the Use of Blood by Physicians and Surgeons

National Survey of Knowledge and Attitudes of Physicians and Surgeons toward Blood Resources and Use This study seems absolutely necessary. Although we might well be able to survey some of the larger medical centers and make estimates about the ways in which physicians and surgeons view blood use, we need data on physicians and surgeons from all geographic areas and all types of practices. Such a national survey could be directed by the medical-education division of a large medical school or by a commercial agency.

Survey of Arguments to be Used in the Introduction of Change This study is similar to that to be used on the general population. A survey of the available arguments as they have been used in successful blood component therapy programs would be productive.

Experimental Study of Effective Message Techniques Physicians and surgeons receive messages in ways somewhat different from the general population—they are visited by representatives of pharmaceutical houses, they attend professional meetings, they read medical journals and attend hospital staff meetings. It seems desirable to test various message strategies on sample populations of physicians and surgeons with a view to examining the effectiveness of particular messages in inducing changes in attitude and behavior toward the use of blood components.

Studies of Change in Medical Education It may be that our system of transmitting information about proper blood use needs careful examination to ensure that all physicians and surgeons are exposed systematically to the most modern knowledge. It is possible that this should be done during formal coursework, it is possible that it is more effective if conducted during residency training, and it is possible that it is better if delayed until specialty training. In any case, some careful study of national practice seems necessary if we are to develop proper utilization of our blood resources.

References

1. American Association of Blood Banks. Physician's Handbook of Blood Component Therapy. Chicago: American Association of Blood Banks, 1969. 63 pp.
2. American Medical Association. Digest of Official Actions–1846-1958. Chicago: American Medical Association, 1959. p. 74.
3. American Medical Association. Directory of Blood Banking and Transfusion Facilities and Services. Chicago: American Medical Association, 1969. 79 pp.
4. American Medical Association Committee on Transfusion and Transplantation. Red blood cell transfusions. JAMA 212:147, 1970.
5. American Medical Association House of Delegates. Position statement on definition of blood as a medical service, p. vii. In American Medical Association. Directory of Blood Banking and Transfusion Facilities and Services. Chicago: American Medical Association, 1969.
6. *Blank* v. *United States,* 400 F. 2d 302 (5th Cir. 1968).
7. *Carter* v. *Inter-Faith Hospital,* 304 NYS 2d 97 (1969).
8. Commission on Drug Safety. Report of the Commission on Drug Safety. Washington, 1964. p. 18. (Available from Federation of American Societies for Experimental Biology, Washington, D.C.)
9. *Community Blood Bank* v. *Federal Trade Commission,* 405 F. 2d 1011 (8th Cir. 1969).
10. Executive Office of the President, Office of Defense Mobilization. National Blood Program. Washington: February 1952.
11. National Communicable Disease Center. Hepatitis Surveillance Report No. 31. Atlanta: National Communicable Disease Center, 1970. p. 21.
12. National Heart Institute Heart Information Center. The National Heart Institute's National Blood Resource Program. Washington, D.C.: Government Printing Office, 1969. 34 pp.
13. Pert, J. H. The Tri-City Pilot Project: A Community Program of Improved Blood Utilization. New York State Department of Health, Division of Laboratories and Research, January 1970. 16 pp. (unpublished)
14. Strumia, M. M., W. H. Crosby, J. H. Gibson 2d, T. J. Greenwalt, and J. R. Krevans, Eds. General Principles of Blood Transfusion. Philadelphia: J. B. Lippincott Co., 1963. 45 pp.