

Uses and abuses of plasma therapy in the patient with recurrent infections

Michael E. Miller, M.D. *Los Angeles, Calif.*

This review summarizes the current guidelines for the use of plasma therapy in patients with recurrent infections. Only the two major groups of proteins of present therapeutic significance are discussed. These are the immunoglobulins and the complement components.

Increasing knowledge of the clinical disorders associated with recurrent infections has led to a variety of innovative therapeutic approaches. When compared with reports of marrow transplantation, lymphoid system reconstitutions, and administration of transfer factor, however, the use of plasma or plasma products in the treatment of patients with recurrent infections has received relatively little attention. This is unfortunate for two reasons. First, several of the newer uses of plasma constituents must certainly be included among the more exciting therapeutic advances in the field. Second, the hazards of indiscriminate use of plasma constituents are very real ones, and the decision to use plasma therapy in a particular patient cannot be relegated to the philosophy of, "We might as well try it, since no harm will result."

The purpose of this review is to summarize the current guidelines for the use of plasma therapy in the patient with recurrent infections. While many agents of *potential* therapeutic importance are present in plasma, we shall discuss here only the two major groups of proteins that are of *present* therapeutic significance in such disorders, i.e., the immunoglobulins and the complement components.

IMMUNOGLOBULIN REPLACEMENT—USES AND ABUSES

The modern era of clinical immunology derives from the description by Colonel Ogden Bruton¹ of a boy with recurrent infections, diminished levels of circulating immunoglobulins, and a dramatic response to the intramuscular administration of pooled human gamma globulins. An unfortunate outgrowth of this report was that gamma globulin became a panacea for any child with undue susceptibility to infections. Despite increased understanding of the complexities and spectrum of immunologic disorders, the use of gamma globulin therapy in clinical medicine still far exceeds the indications. In order to define

From the Department of Pediatrics, Charles R. Drew Postgraduate Medical School.

Presented in part at the Postgraduate Course of the American Academy of Allergy, San Francisco, Calif., Feb. 5, 1972.

Received for publication Sept. 1, 1972.

Reprint requests to: Michael E. Miller, M.D., Department of Pediatrics, Charles R. Drew, Postgraduate Medical School, 1620 E. 119th St., Los Angeles, Calif. 90059.

those situations for which gamma globulin is specifically indicated, it is necessary first to summarize current knowledge regarding the preparation and measurement of immunoglobulins.

Gamma globulin preparations

Intramuscular administration. Preparations of human pooled serum immunoglobulins for intramuscular use are available from some 15 to 20 manufacturers. All of these are prepared by the cold ethanol precipitation method of Cohn.² This method has undergone little modification in this country since the original description some 25 years ago. The major advantages of the Cohn fractionation are: (1) The use of ethyl alcohol as precipitant. In addition to being cheap, this permits the preparation to be carried out below the freezing point of water, thereby minimizing the risk of microbial contamination. (2) Upon precipitation of protein in relatively small volumes, the alcohol can be removed rapidly by lyophilization. (3) The method permits manipulation of precipitating conditions, thus permitting separation of proteins on the basis of solubility characteristics. (4) Hepatitis virus is removed. This offers a distinct advantage over the use of plasma therapy in the replacement of immunoglobulins.

Gamma globulin as prepared by the Cohn method is a viscous material that requires an 18 to 20 gauge needle for administration. The gamma globulin content is approximately 165 mg. per milliliter (16.5 per cent).

Intravenous preparations. For many reasons, the development of a safe, yet effective, intravenous preparation of gamma globulin has long been sought. First, in the patient on gamma globulin therapy, the maintenance dosage is in the range of 0.6 ml. per kilogram. This means, for example, that an adolescent male with hypogammaglobulinemia might require as much as a 30 to 60 ml. volume of fluid injected intramuscularly every 3 weeks. Second, intramuscular preparations contain insignificant amounts of IgA or IgM. Finally, if large quantities of immunoglobulins need to be administered rapidly, an intravenous preparation would be desirable.

There have been 2 major problems in the development of suitable intravenous preparations. First, such preparations often have the tendency to undergo rapid aggregation upon administration, resulting in the occurrence of severe local or systemic reactions. Second, although the incidence of such reactions can be reduced by certain modifications of the molecule such as acid or pepsin treatment, the in vivo half-life of molecules so treated is usually much reduced, often to less than 24 hours. At the present time, there are no intravenous preparations that satisfy these two objections and that have demonstrably improved the therapeutic response over the intramuscular route.³ The current usage of intravenous gamma globulin preparations is restricted to certain ongoing, acute infections, rather than for prophylaxis in hypogammaglobulinemia. Treatment of immunoglobulin molecules with human fibrinolytic, caprylate, kaolin, or bentonite results in removal of aggregates but does not destroy the Fc fragments of the molecules. Such methods may, in the future, produce a suitable preparation of immunoglobulins for intravenous use.

Replacement of immunoglobulins by plasma infusion. A wider range of

immunoglobulins than in intramuscular preparations can be administered to a patient through plasma infusions. The significant problem of transmission of hepatitis through such therapy can, to a degree, be minimized by the use of a "buddy system" whereby plasmaphoresis is done regularly in a few donors who are screened carefully and serve as the only source of plasma for the patient.⁴ In addition to providing a means for replacing large quantities of immunoglobulins, this form of treatment may be of advantage in the hypogammaglobulinemic patient suffering from persistent pulmonary disease or recalcitrant diarrhea.

The disadvantages of this method are the risk mentioned previously of transmission of hepatitis and the inconvenience caused by the preparation and administration of plasma. At the present time, however, plasma infusions are the only effective method of administration of IgM.

Measurement of immunoglobulins

In order to treat immunoglobulin deficiency adequately, accurate measurement of immunoglobulin levels is obviously important. Simple as this statement may seem, errors in the quantitative measurement of immunoglobulins are all too frequent. These generally fall into 2 major categories:

Inadequacy of method. Immunoglobulins are usually evaluated by one of 3 methods, serum electrophoresis, immunoelectrophoresis, and quantitative immunodiffusion. Serum electrophoresis remains one of the most overused tests in laboratory evaluation. It is, at best, a screening test of a semiquantitative nature. Further, it tells one little of the makeup of individual immunoglobulin classes. Immunoelectrophoresis is also a semiquantitative method. One can learn much of the qualitative nature of immunoglobulins from the are patterns. With the exception of gross excesses or almost total absence of immunoglobulins, however, it is a notoriously inaccurate method for quantitative evaluation. The most widely used, and fairly accurate, quantitative method is the radial diffusion method.⁵ The accuracy of this method is adequate for clinical evaluation.

Failure to utilize age-related standards

This is, perhaps, the single most common source of error, particularly within the pediatric age group. Far too many children are diagnosed as having "borderline low" values of immunoglobulins based upon adult standards, when the values obtained are normal for age.⁶ It is also essential that the standards of comparison be those of a particular laboratory that is performing the tests. Variability of results obtained from one manufacturer to another or among technical personnel carrying out the tests may be significant. Differences in immunoglobulin levels among various ethnic groups must also be taken into account.⁷

Hazards of immunoglobulin therapy

For a number of reasons, the unnecessary use of gamma globulin should be discouraged:

1. As we have indicated previously, a teen-age boy being treated for hypo-

gammaglobulinemia may, theoretically, require in the range of 30 to 60 ml. volume injected intramuscularly approximately every 3 weeks. This is an extremely painful procedure and should be avoided if possible. Even in smaller children, the relative amounts of material injected are often the source of great discomfort.

2. Cost and availability of gamma globulin preparations will be affected by widespread increases in utilization. For example, pooled human gamma globulin was formerly available at no cost from the American Red Cross. Presently, however, patients with hypogammaglobulinemia must purchase their gamma globulin, either at personal cost or through some clinical research program. Were the use of gamma globulin to become more widespread, say for children with recurrent respiratory infections (see below), significant increases in cost and decreases in supply would result.

3. Sensitization may occur to repeated injections of gamma globulin.⁸ Each injection of pooled human immunoglobulins contains multiple foreign proteins that, although having antibody activity, also serve as antigens to the recipient. The reactions that may occur encompass a wide range and may, on occasion, be extremely severe.

4. The development of active immunity may be impaired in the patient receiving repeated injections of gamma globulin.

5. Perhaps the most compelling argument against the indiscriminate use of gamma globulin therapy is the creation of what we term the "gamma globulin cripple." By this I refer to the exceedingly common situation created when a child with recurrent infections is inappropriately placed upon a "trial" of gamma globulin therapy in the interest of "seeing what will happen." Far too often the parents conclude that their child is "fragile" and not able to keep pace with peers. The gamma globulin becomes lifesaving to the extent that once such a pattern has been established, the physician may be unable to stop the therapy. The psychologic trauma that this often brings upon a child and his parents cannot be overstressed and offers a strong argument against introduction of gamma globulin on the "clinical trial" basis.

Uses of gamma globulin

Based upon the preceding remarks, one might conclude that gamma globulin is a useless preparation. This is not quite true. There are specific indications for which gamma globulin may be highly effective. These are summarized in the following paragraphs.

Primary immunodeficiency states. In primary humoral immune deficiency states, such as Bruton's disease, gamma globulin therapy may be highly effective. There are, however, relatively few such situations. In clinical states in which cellular immunity is defective, either combined with, or exclusive of, immunoglobulin deficiency, gamma globulin injections, while not contraindicated, are unlikely to be effective.⁹

Viral and bacterial prophylaxis. This area provides a number of indications for gamma globulin therapy. The various indications and dosages have recently been reviewed.^{10, 11}

Secondary hypogammaglobulinemia. Immunoglobulin levels may be significantly decreased secondary to some other primary disorder, for example, protein-losing enteropathy. In such situations, *with quantitative evidence* that IgG levels are at hazardously low levels (less than 200 mg. per cent), gamma globulin therapy is indicated. Emphatically, however, primary attention should be directed toward diagnosis and treatment of the basic disorder, and gamma globulin therapy should be discontinued as soon as possible.

Potential uses of gamma globulin. There are several areas that may, in the near future, provide an expanded use for gamma globulin therapy. The first of these involves the use of locally introduced preparations, particularly in the respiratory and gastrointestinal tracts. Part of the problem involves the isolation of IgA in adequate amounts for commercial preparation. That obtained from plasma is, in general, deficient in the secretory piece of the molecule. While the role of this portion of the intact IgA molecule is presently unclear, it appears that full functional activity of IgA is lacking in preparations obtained from plasma. The introduction of immunoglobulins via such vehicles as snuffs or direct instillation into the gastrointestinal tract has thus far been unsuccessful.

Further future potential lies in the development of antibody preparations that would complex with host antibodies against foreign antigens. For example, a specific anti-IgE preparation against ragweed antibodies might be able to complex all of the host's antibodies against ragweed and thereby prevent the initial antigen-antibody reaction that ultimately triggers an allergic response. While formidable problems still exist in the development of such therapeutic approaches, they are at least theoretically feasible.

Another area that is developing more rapidly is the expanded use of high-titer immunoglobulin preparations in the prevention of specific infections.¹²

Misuses of gamma globulin

Some of the more frequent misuses of gamma globulin therapy are discussed in the following paragraphs.

Prophylaxis of infection in the normal neonate. Despite ample evidence to the contrary, many physicians continue to utilize gamma globulin therapy in the management of the normal neonate. This makes little sense, either on clinical grounds or on a theoretic basis. IgG is the only maternal immunoglobulin group placentally transferred to the fetus. Further, it appears that the entire IgG group of molecules is passed. Since intramuscular immunoglobulin preparations contain, almost exclusively, IgG, there is no rationale at the present time for its routine administration to neonates. Clinical studies have confirmed the ineffectiveness of gamma globulin therapy in protecting normal neonates from significant infections.¹³

With regard to very low birth weight premature infants, the data are unclear.^{14, 15} At the present time, the best recommendation is that quantitative measurement of immunoglobulins be performed in any premature infant for whom gamma globulin therapy is considered.

If one is faced with a septic, or high-risk newborn, then the therapy of

choice is plasma or blood rather than intramuscular gamma globulin. These preparations will give the infant IgM as well as IgG.

Treatment of viral infections. There is, unfortunately, a continuing misconception that administration of immunoglobulins may be of use in the recovery from viral-induced illness. There are ample clinical studies demonstrating that such is not the case. The use of gamma globulin in viral infection is restricted to prophylaxis and prevention for defined periods after exposure to individual viruses. Once clinical infection has occurred, gamma globulin is totally ineffective.

Asthma. Gamma globulin is ineffective in the treatment or prophylaxis of bronchial asthma.¹⁶ While this is a frustrating disorder for the patient, the family, and the physician to manage, there is no justification for the introduction of another ineffective agent into the regimen.

Recurrent respiratory infections. It is within this clinical area that the greatest abuse of gamma globulin therapy occurs. The child who is referred because of recurrent upper respiratory infections presents one of the most frustrating clinical problems confronted by the pediatrician. When one excludes the very small number of such children who turn out to have a specific immunodeficiency state or an obvious allergic diathesis, there remains a large number of patients who lack any specific cause for their infections. In the typical case, the infections are most probably viral in nature. The children grow and develop normally and enjoy normal health between episodes. The idea that gamma globulin might be of therapeutic benefit in such patients derived from recognition of the role of IgA in local immunity of the respiratory tract. It was postulated that children with recurrent respiratory infections might be deficient in IgA and, hence, might show an improved clinical picture upon administration of gamma globulin. There are two major problems with this reasoning. First, as has been pointed out, there is little functionally active IgA present in pooled gamma globulin preparations. Second, there is no documented evidence of decreased local or systemic immunity in such patients.

Studies purporting to show IgA deficiency in such patients and a subsequent favorable clinical response to the administration of gamma globulin suffer from a range of errors of interpretation and methodology.^{17, 18} The problem is compounded by the possibility that, among a large group of children with recurrent respiratory infections, a few may have specific defects that respond to gamma globulin therapy. Deficiencies of one of the IgG subgroups, for example, might be overlooked on quantitative determinations, yet respond to such therapy.¹⁹ The number of such patients, however, is exceedingly small and certainly does not justify the widespread clinical trial of gamma globulin therapy in children with recurrent respiratory infections. It is particularly within this group that the hazard of creating the "gamma globulin cripple" is so great.

Dosage errors. There are a variety of errors made in the amount and frequency of gamma globulin injections: (1) The initial dosage may be correct, but the physician fails to adjust the dosage over time, so that the child "outgrows" effective treatment and is erroneously considered to have become resistant to therapy. (2) The patient is placed on such a low dosage of gamma

globulin that no therapeutic benefit could result. The idea that "low-grade infections don't require much gamma globulin" is totally unsupported. (3) Too long an interval is established between dosages. The current recommendations for gamma globulin therapy are based upon an average half-life of exogenously administered IgG of 3 weeks. The dosage schedule is based upon achieving a blood level of approximately 400 mg. per cent, which, assuming a normal 3 week half-life, would keep the minimum level of IgG at approximately 200 mg. per cent.²⁰ The latter appears, on the basis of long-term experience with hypogammaglobulinemic patients, to be the minimum effective level in protection against infection. The administration of appropriate dosages at intervals of greater than 3 to 4 weeks, therefore, may result in many periods when the patient is not adequately protected against infection. (4) Adherence to an "absolute" dosage regimen. Gamma globulin preparations are not rigidly standardized. The protein content of a particular preparation containing immunoglobulin activity may vary from 12.5 to 16.5 per cent. Within this fraction, the amount of IgG, IgA, and IgM also varies considerably from one manufacturer to another.²¹ Finally, the amount of any specific antibody in such preparations is variable and entirely unpredictable. It, thus, makes little sense to adhere to rigid intervals between injections, say 28 days. This is likely to produce considerable anxiety in the mother and the child, who begin to imagine all sorts of signs and symptoms developing when a dosage is overdue, sometimes by as little as hours. Any patient placed upon gamma globulin therapy must be individually evaluated. Some require injections more frequently than at 3 week intervals, while some may do perfectly well on an every 4 week regimen. The recommended dosages and frequency of injections should be recognized as guidelines to be worked around depending upon individual patient needs.

THERAPY OF DEFICIENT COMPLEMENT-MEDIATED SUSCEPTIBILITY TO INFECTIONS—A DEVELOPING FIELD

The recognition that other humoral factors besides immunoglobulins play a significant role in host resistance to infections has been a major development of the past decade. Of the other factors involved, those of the serum complement system have been the most widely studied. While the successful replacement of complement components in human disease is limited at the present time, the future potential of this area should add considerably to our success in treatment of the patient with recurrent infections.

The complement system has been the subject of several excellent reviews,^{22, 23} and only a brief summary will be offered here.

Eleven distinct proteins have presently been identified within the complement system. Of these, 3 are activated to form the first active component, or C1, of the system. Following activation of the first component, the remaining 8 components sequentially interact. The numerical designation of the components is the result of an attempt to standardize the nomenclature, thereby avoiding confusion similar to that which has resulted from a variety of terminologies of the clotting system. This has been only partially successful, however, as the components have been numbered as they were described, which turns out

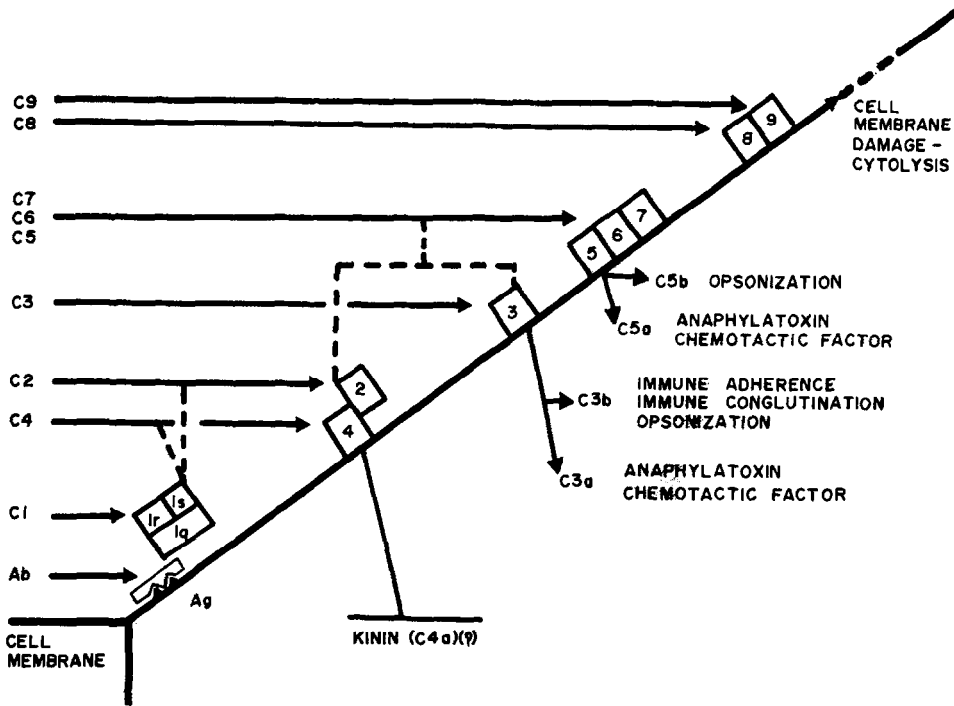


FIG. 1. The human complement system. For details see text.

not to be their exact order of reaction. Hence, the order of reaction is C1, C4, C2, C3, and then, in order, C5 through C9. Among the means by which the system can be activated, the most widely recognized trigger is the forming of an antigen-antibody complex. Activation of the complement system by this mechanism is diagrammatically represented in Fig. 1. The diagonal line represents a cell membrane, for example, that of a particular bacterium.

If the host possesses an antibody against that particular organism, an antigen-antibody complex will be formed. If the antibody involved is one of the many that are capable of fixing or activating complement, then the components sequentially interact upon the cell membrane-antigen-antibody complex. In the course of these reactions, three basic types of biologic activity are involved. The first of these is represented by the classical model of sheep red blood cell hemolysis, which forms the basis for study of the complement fixation reaction. In this situation, a sheep red blood cell against which specific antibody has reacted is lysed by the action of the complement system upon the cell membrane. The mechanism for this lysis appears to depend upon specific enzymatic attack on the lipid surface, resulting in a defect or "hole" being punched in the membrane. The consequence of these events is an osmotic lysis of cell. This type of reaction is the first major type of reaction of the complement system, i.e., the sequential reaction of all components resulting in membrane damage. Although sheep cell hemolysis represents the model for this type of reaction, such a sequence can probably take place upon a variety of cell membranes, so that a

situation is provided by which complement can bring about membrane damage. This need not result in hemolysis, as in the case with red cells, but could result in other forms of cell damage to bacterial cells, tumor cells, or even normal body cells. The potential clinical spectrum produced by such a mechanism is unknown at the present time but is obviously very broad.

The second mechanism by which complement results in biologically significant alterations of the inflammatory system concerns the effects upon the antigen-antibody-membrane complex as the sequential interaction of the components upon the membrane takes place. During the process, the membrane is changed by either structural, conformational, or physicochemical means, the result being that the entire complex is better attacked or recognized by the inflammatory system. For example, when the components have reacted through the C3 stage, a particle such as a pneumococcus has been "opsonized" or, in other words, can be better phagocytized by a particular phagocyte in the area. The clinical applications of such a sequence will be discussed shortly.

The third mechanism of basic biologic significance involving the complement sequence is the most poorly classified but may ultimately prove to be of the most widespread clinical significance. During the reaction of the individual components upon the membrane, enzymatic or cleaving reactions are taking place upon the components as they exist in their native state. In the process, small pieces of the native molecule are split off and are free to circulate in the plasma. Unlike the native molecules, these low molecular weight split products often have significant biologic activities. For example, such a product of the third component, so-called C3a, has at least 2 recognized biologic activities. The first of these is mediated by the release of histamine through appropriate tissue receptors via a material known as anaphylatoxin. A broad range of biologic events may be mediated through such a process, and obvious therapeutic benefit would result through more complete understanding of the system. A second known biologic activity of C3a is in chemotaxis. It plays a role in the attraction of white blood cells to a focus of inflammation. Again, such an activity has obvious potential throughout a wide range of biologic activities.

The classical antigen-antibody mediated pathway that we have reviewed is not the sole means of activation, nor do all activations of the pathway involve the entire chain of reactions. It appears, for example, that, under certain conditions, endotoxin can activate the sequence directly at the C3 level. The concept of alternate pathways, as proposed by Gewurz some years ago, is proving to be of major clinical import. As an extension of these concepts, it should be noted that a variety of other systems, such as the kinin system, are also capable of activating the complement system. Thus, the idea that we shall be fortunate to find a large group of inflammatory deficiency syndromes mediated by isolated deficiencies of a particular component of a particular system is oversimplified. Still, as knowledge of the pathways involved in inflammation and of their various interactions increases, we would be better able to approach the clinical diagnosis and therapy of the inflammatory deficiency syndromes.

Through this brief review of the functional and biologic activities of the complement system, it should be apparent that a rather broad clinical area has

been defined in which the therapeutic replacement of individual or groups of complement components may enhance the management of many patients with recurrent infections.

The first disorder to be considered is an inborn error of the complement system in which therapeutic success has been partially achieved. While this remains the only such success to date, it seems likely that in the future other defects involving the system will be identified and successfully treated. This disorder was first described in 1968.²⁴⁻²⁶ To date, there have been 4 positively identified kindreds. In each case the afflicted children presented with diarrhea, generalized seborrheic-like dermatitis, recurrent infections, and failure to thrive. In these families, a deficiency of opsonic activity involving a dysfunction of the fifth component of complement has been demonstrated through the use of a sensitive assay of phagocytosis that measures the number of bakers' yeast particles taken up by leukocytes. Since the uptake of these particles requires opsonization, the assay may be used to measure either leukocyte activities or humoral opsonic activity. In these patients and their affected relatives, a deficiency of phagocytosis-enhancing activity of sera toward yeast particles can be restored to normal by the addition of highly purified preparations of the fifth component of complement, or C5. Also, serum from mice with a genetic deficiency of C5 gives poor enhancement of yeast uptake, and the addition of highly purified C5 to C5-deficient mouse serum restores phagocytosis-enhancing activity. Finally, the addition of C5-deficient mouse serum to the patient's serum fails to improve the opsonic activity of the patient's serum, whereas the addition of small amounts of normal mouse serum does improve the opsonic activity.

The institution of fresh plasma infusions to each patient has resulted in dramatic clinical improvement.

The clinical course of these children shares certain similarities with the syndrome described by Leiner in 1908.²⁷ Upon review of his cases, it now appears that the syndromes of C5 deficiency and of Leiner's disease are one and the same. This represents a clinical entity of importance to the clinician, since effective, potentially lifesaving therapy can be instituted. Present therapy of this disorder requires infusion of material containing opsonically active C5. *Fresh* plasma or blood satisfies these requirements, while refrigerated plasma or blood over 24 hours old does not. It is hoped that isolation of a semipure preparation of C5 will eventually replace the need to utilize whole blood or plasma transfusions in the treatment of these patients.

The dramatic clinical success that has been achieved in C5 dysfunction underscores the basic introductory comments involving both "uses" and "abuses." The application of basic clinical and laboratory observations has led to a reasonably specific "use" of plasma therapy in a patient with recurrent infections. At the same time, it should be emphasized that the use of whole blood or plasma in treatment of a disorder of a single protein is not optimal.

Ongoing investigations into a number of other complement-mediated defects resulting in recurrent infection may soon increase the therapeutic applications of replacement therapy.²⁸⁻³⁰ As this field develops, it is important to avoid the

numerous abuses that have occurred with gamma globulin replacement. In particular, the indiscriminate use of plasma therapy in a patient with recurrent infection is to be avoided.

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